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ANESTHESIOLOGY CLINICS OF NORTH AMERICA

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New Developments in Pediatric Anesthesia

Jerrold Lerman, MD, GUEST EDITOR

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Cumulative Index 1991 **933**

Subscription Information **Inside back cover**

FOREWORD

Administering anesthesia to a very small pediatric patient can be a frightening and anxiety-provoking experience even for experienced pediatric anesthetists. Pediatric patients may face the impending surgery with important physiologic and anatomic problems (e.g., impaired thermal regulation, precarious fluid and electrolyte and caloric balances, altered airway anatomy, cardiovascular instability, altered control of breathing, and difficult intravenous access. The impending surgery as well may cause major physiologic intervention such as repair of numerous congenital defects involving the heart, trachea, esophagus, lung, diaphragm, gastrointestinal track, spinal column, and so forth. Fortunately, the quality of anesthetic care for infants and children has improved dramatically in the last decade; the improvement has resulted from both basic and clinical research in physiology, pathophysiology, pharmacology, monitoring, and the introduction of new anaesthetic drugs and techniques. This issue of *Anesthesiology Clinics of North America* on "Pediatric Anesthesia" summarizes all of the advances on all these pediatric anesthesia frontiers.

Dr Jerrold Lerman is a highly credentialed guest editor. The medical machinery at The Hospital for Sick Children, Toronto, Canada, functions well because of Dr Lerman's input; he is the Anesthetist-in-Chief of his department and as such chairs and is a member of many medically important committees. Dr Lerman is also an outstanding teacher. He has won the best clinical instructor award at The Hospital for Sick Children, is on various departmental and hospital education committees, has organized various anesthesia and American Academy of Pediatrics meetings, and has extensively lectured on many pediatric anesthesia subjects at many prestigious national and international meetings. Finally, and most importantly, Dr Lerman is a well-funded, well-respected, and presently, a very productive researcher. He has produced high quality research, published in the most reputable journals, on most of the advancing frontiers of pediatric anesthesia. He has an astute clinical mind that asks clinically relevant questions, and he is primarily a clinical researcher whose ideas are inspired by clinical problems. As a consequence of his research productivity, he is co-director of anesthesia research at The Hospital for Sick Children and is on various important scientific and editorial advisory boards. Thus, Dr Lerman's administrative, teaching, clinical care, and research profile eminently qualify him to guest edit this issue of *Anesthesiology Clinics of North America* on "Pediatric Anesthesia." In view of the compelling clinical nature of the issue and the expertise of the guest editor, it is certain that reading this issue will be a valuable experience and aid to the administration of pediatric anesthesia for all anesthesiologists.

JONATHAN L. BENUMOF, MD
Consulting Editor

FORTHCOMING ISSUES

March 1992

EPIDURAL AND SPINAL ANALGESIA AND ANESTHESIA
M. S. Batra, MD, *Guest Editor*

The last few years have witnessed a dramatic renewal of interest in regional anesthesia. The reasons for this renewed interest include the introduction of new equipment, techniques, and drugs; increased applications of neural blockade; greatly expanded use of regional anesthesia in the management of postoperative pain, and the demonstration that regional anesthesia decreases surgical morbidity, hospitalization time, and expense. The guest editor of this issue, Dr M. S. Batra, is nationally and internationally recognized as an expert in the field and is very actively involved in the activities of several organizations that teach and promote regional anesthesia. This issue of *Anesthesiology Clinics of North America* on "Epidural and Spinal Anesthesia and Analgesia" is, consequently, very timely, important, and valuable in its concepts and clinically relevant practical instruction and is therefore a compelling issue for all anesthesiologists to read.

June 1992

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September 1992

CEREBRAL PROTECTION, RESUSCITATION, AND MONITORING:
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EMBOLISM AND ANESTHESIA
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September 1991

MYOCARDIAL ISCHEMIA AND PERFORMANCE
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June 1991

CRITICAL ISSUES IN CRITICAL CARE
Vladimir Kvetan, MD, and T. James Gallagher, MD,
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March 1991

FIBEROPTICS IN ANESTHESIA
James T. Roberts, MD, *Guest Editor*

December 1990

PREANESTHETIC ASSESSMENT
Elizabeth A. M. Frost, MD, *Guest Editor*

PREFACE

Many of the recent exciting advances in modern medicine have occurred in pediatric anesthesia. This issue of *Anesthesiology Clinics of North America* entitled "New Developments in Pediatric Anesthesia" summarizes some of these developments for the practicing anesthesiologist.

In the past, the usual practice had been for innovative concepts in anesthesia to be introduced in adults and then, after often a lengthy delay, in turn to infants and children. In most instances, research and development were restricted to the adult age group, and rarely, if ever, were they undertaken in children. In the last 5 to 10 years, however, this traditional approach has changed. Today, research and development in medicine concentrate not only on adult issues but also on those pertinent to the infant and child. New drug development, regional anesthesia, pain management, and extracorporeal membrane oxygenation are but a few of the examples of programs discussed herein in which pediatric anesthesia has established itself on the cutting edge of our specialty.

This issue is not intended as a comprehensive review of pediatric anesthesia, but rather a synopsis of those aspects of our specialty in which there have been significant advances. Indeed, the mandate assigned to each author was to review briefly the current understanding of their subject and then discuss thoroughly the relevance of recent advances to pediatic anesthesia.

Twelve of North America's leading pediatric anesthesiologists are contributors. Each is a recognized expert and authority in his or her subspecialty. As you reflect on the articles presented, I think you will appreciate how effectively each of the authors combined advances in research with clinical developments to offer a balanced and comprehensive overview of his or her subject.

The future in pediatric anesthesia has never been more promising. Much has already been accomplished, but many more challenges lie ahead. It is my hope that this issue of the *Anesthesiology Clinics* contributes to our understanding of pediatric anesthesia and thereby improves our care of the small patients placed in our charge.

JERROLD LERMAN, MD, FRCPC
Guest Editor

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New Developments in Pediatric Anesthesia 0889–8537/91 $0.00 + .20

Preoperative Fasting and Medication in Children

*John E. Morrison, Jr, MD, FAAP,**
and Charles H. Lockhart, MD, FAAP†

> Empirical procedures firmly entrenched in the habits of good doctors seem to have a vigor and life, not to say immortality, of their own.‡
>
> BEECHER

In the past it had generally been the custom among anesthesiologists to arrange for pediatric patients scheduled for elective surgery to present to the operating room having been fasted for at least 6 hours and heavily premedicated. With the advent of day-surgery scheduling and facilities, increased participation of parents in their child's anesthetic experience, and the elimination of anesthetics such as diethyl ether in the United States and Canada, such preanesthetic protocols have been questioned or eliminated.[15, 18, 53] This article reviews the rationale for fasting and premedication in children presenting to the operating suite and some pertinent literature, and suggests recommendations for management of the specific pediatric patient.

HISTORICAL PRECEDENT

During the early and midtwentieth century the use of chloroform and diethyl ether was associated with prolonged induction times, copious secretions, vomiting, and prolonged recovery periods. Eckenhoff[21] described significant personality changes in 17% of pediatric patients associated with the hospital anesthetic experience including onset of night terrors, fear phenomena (e.g., fear of odors, strangers, and having the face covered), and bedwetting, which he was able to associate with use of a specific agent: divinyl ether. Faced with such difficulties, it was not unreasonable to include medications in the anesthetic plan that would minimize side effects of the primary anesthetic agents and facilitate the induction of and emergence from anesthesia for *both* the patient and the anesthetist. The use of atropine, scopolamine, and morphine increased in popularity, and the presence of a heavily sedated patient with a dry mouth was considered a desirable outcome on

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‡*From* Beecher HK: Measurement of Subjective Responses: Quantitative Effects of Drugs. New York, Oxford University Press, 1959; with permission.

arrival in the operating room. With the emergence of newer agents (e.g., thiopental, halothane) in the late 1940s and 1950s, the induction of anesthesia became quicker and less difficult, the side effects (e.g., vomiting, prolonged somnolence, dysphoria) of the premedicant drugs themselves became more notable and less desirable, and the objective of premedication focused on the reduction of patient apprehension.[46, 98] A plethora of clinical studies undertook the challenge to identify the ideal drugs(s), dosage(s), and technique(s), which continues to this day.[1, 6, 25, 46, 84, 98] Only recently has the necessity of the prolonged fasting period associated with the use of the older anesthetics come to be questioned.[15, 17, 54, 74]

THE CHILD AND THE ANESTHESIOLOGIST

> Children tend to show an alert appearance, active temperament, and considerable curiosity. The curiosity is often fearful, rather than inquisitive in nature. Their natural degree of cooperation can be spectacularly variable.*
>
> STETSON ET AL

The safe induction of anesthesia in the pediatric patient with a minimum of stress and risk for the child continues to be a reasonable goal. To this end, however, the pediatric patient differs from the average adult who desires primarily lack of recall (amnesia) and relief of anxiety (anxiolysis).[98] Children's anxiety may focus on major issues such as separation from parents, fear of needles, a concern of change in bodily image or not awakening at the end of an anesthetic (i.e., death),[1] or seemingly minor issues such as taste or odor of medications, and the size of tablets or capsules.[21]

The anesthesiologist caring for the child, primarily interested in minimizing potential risk factors during the anesthetic, may be more concerned about prevention of secretions, decreased vagal activity, vomiting and aspiration, medication overdose and respiratory depression as a result of a premedication order,[84] and assessment of an acceptable airway.

To attain these varying ends our specialty is presently involved in a potpourri of approaches (e.g., psychological preparation including play therapy and preoperative tours of the surgical facility, assessment of various premedications and techniques, and review of our assessment of risk factors such as the relationship of preoperative fasting to perioperative aspiration) to best prepare the child and parents for the anesthetic experience.

PEDIATRIC RISK FACTORS: ASPIRATION

In a 1964 review of pediatric anesthesia mortality, Graff et al[29] reported that 26% of the deaths were due to aspiration of vomitus or blood. However, three recent large studies have shown a remarkably low incidence of aspiration during anesthesia in the pediatric population.[5, 60, 92] In a prospective study of 40,000 anesthetics in France, Tiret et al[92] reported only four episodes of aspiration, two of the cases occurring during anesthesia and two during the recovery period. In the United States, Nicholson et al[58] mentions an incidence of 2 in 40,000, whereas in a prospective study Borland et al[5] found an incidence of aspiration of only 0.17% (25/14,991) with half the children classified as ASA category III or IV. Healthy children (ASA I or II) had an incidence of only 0.09%, and all recovered uneventfully. Within the aspiration group Borland et al noted that three children had a prior history of esophageal surgeries, and two were known to vomit during previous inductions.

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*_From_ Stetson et al: Use of oral chloral hydrate mixtures for pediatric premedication. Anesth Analg 41:203–215, 1962; with permission.

It appears that the incidence of significant complications of perioperative aspiration in the pediatric population is presently quite low, and that certain patient groups (e.g., prior esophageal surgery) can be identified to be at an increased risk and treated appropriately. Data are scant concerning acute aspiration during anesthesia in potential high-risk groups such as infants with pyloric stenosis or those born prematurely with persistent pulmonary disease, neurologic sequelae (e.g., seizures, hypotonia, and developmental delays), and previously documented aspiration pneumonitis. Other considerations should also be taken into account. For example, adults are reported to have up to 14% "silent" regurgitation during surgery, with an increasing incidence using the narcotic N_2O-relaxant technique (20%), in upper abdominal procedures (29%), and in the prone position (37%).[93]

However, it must be emphasized that in many respects children should be at a much higher risk of complications from aspiration than is reported. Almost all recent studies on aspiration pneumonitis have used the"gold standards" of gastric fluid pH less than 2.5 and volume greater than 0.4 mL/kg as predisposing the patient to higher risk,[65, 90] although such "magic numbers" obtained from animal studies are currently being questioned[67] and were not confirmed for the pediatric population. Measurements in fasted, elective day-surgery pediatric patients have repeatedly shown pH of gastric contents less than 2.5[16, 47, 51, 69, 75] and gastric fluid volumes greater than 0.4 mL/kg[47, 75, 79] in a majority of children. Coté et al[16] reported 96% of pediatric patients, both inpatient and outpatient, had a gastric fluid pH of less than 2.5, whereas 76% demonstrated both a pH of less than 2.5 and a volume greater than 0.4 mL/kg. Salem et al[70] have identified several factors in infants and children that predispose them to potential aspiration: higher resting intragastric pressure associated with smaller stomachs and encroachment of abdominal viscera, shorter esophagus, incoordination of breathing and swallowing mechanisms in neonates, as well as excessive angulation of the vocal cords facilitating regurgitation by stretching the cricopharynx during laryngoscopy. Exactly why the incidence of clinically significant acute aspiration pneumonitis associated with general anesthesia in the pediatric population seems much lower than expected remains unanswered.

H_2-RECEPTOR ANTAGONIST USE IN PEDIATRIC ANESTHESIA

The hypothesis of a reversible, competitive H_2-receptor antagonist in 1966, functioning to inhibit histamine-mediated production of hydrochloric acid by parietal cells in the stomach, and its synthesis in 1972 provided clinicians with a mechanism to reduce gastric pH.[48] Neonates, infants, and children can be premedicated with H_2-receptor antagonists such as cimetidine[28, 48, 100] or ranitidine[24, 44], but caution must be exercised,[48, 101] particularly if administered intravenously due to associated hypotension and cardiac arrhythmias (i.e., bradycardia). Chhattriwalla et al[13] reported a neonate having reflux esophagitis treated with cimetidine, 10 mg/kg/d for 3 weeks, without complication. Thompson and Lilly,[91] however, cite the onset of severe obtundation in a 2-month-old patient treated with cimetidine, 40 mg/kg/d, which resolved with the cessation of the drug. Bale et al[4] described dysarthria, hallucinations, and altered consciousness in a 4-year-old child with cystic fibrosis taking cimetidine, 15 mg/kg/d. While such chronic administration of these agents may pose potential problems for patients in the perioperative period, the acute administration of a single dose preoperatively may be most helpful. Goudsouzian et al[28] studied oral cimetidine in children and determined in the ED_{50} and ED_{95} resulting in pH greater than 2.5 to be 3.0 and 7.5 mg/kg, respectively. They recommended 7.5 mg/kg orally given 1 to 3 hours preoperatively for the prophylaxis of acid aspiration in infants and children. Yildiz et al[100] recommended administration 2 to 3 hours before induction at a dose of 10 mg/kg orally, and measured peak blood concentrations of the drug at 75 minutes after administration (range, 60–180 minutes) with a mean half-life of 138 minutes (± 18, SD).

Ranitidine is likewise effective in children,[24, 44] yet has fewer side effects than cimetidine[101] due to decreased binding at androgen receptors, hepatic mixed-function oxidase system, and peripheral lymphocytes. This can result in less elevation of propranolol, lidocaine, and diazepam blood concentrations than during concurrent cimetidine therapy. Bradycardia has been reported with intravenous (IV) administration. It can be given orally (2.5 mg/kg), intramuscularly (1–2 mg/kg), or IV (1.25 mg/kg).

Stoelting[87] states that the incidence of clinically significant aspiration of gastric contents in healthy patients undergoing elective surgery is so low that routine prophylaxis is not necessary, and Coté[15] presents the same argument for the healthy child.

DECREASING GASTRIC FLUID VOLUME WITH MEDICATION

Metoclopramide has been reported to be effective in enhancing gastric emptying in children.[44, 59] A typical dose for pediatric patients would be 0.1 mg/kg given either orally, IV, or subcutaneously. Olsson and Hallen[59] used 0.3 mL/kg of metoclopramide intramuscularly in children with trauma and found significantly smaller aspirated gastric fluid volumes. The treated group had mean volumes of 0.9 mL/kg compared with 2.1 mL/kg in the control group. Two of the 29 patients given metoclopramide, however, had both pH less than 2.5 and volume greater than 0.5 mL/kg.

Glycopyrrolate has been reported to reduce the volume of gastric secretions at a dose of 7.5 to 10 μg/kg,[28] but to be less effective than cimetidine, and to have no potentiating effect when added to that drug.[47] Salem[69] demonstrated that glycopyrrolate at the same dose reduced gastric fluid volume by 67% and is superior to either atropine or scopolamine.

Antacids have been traditionally difficult to administer to children in the preoperative setting,[28] despite the well-known propensity of children to swallow caustics, kerosene, etc., given the least opportunity.

FASTING: HOW LONG NPO

Several editorials[15, 53, 74, 87] and many recent papers[17, 54, 72, 75, 79–81] have been published questioning the legitimacy of the traditional 6-hour fasting period before elective induction of anesthesia in healthy patients. The underlying question in this area has been, "Does a prolonged fast per se affect the gastric fluid volume and/or pH?" and thus minimize the potential for aspiration pneumonitis. In 1983 Miller et al[54] reported that a "light theatre breakfast" [i.e., buttered toast, tea, or coffee (with milk)] 2 to 4 hours preceding elective gynecologic surgery did not alter volume or pH of gastric contents aspirated through a tube following induction of anesthesia. In 1989 and 1990, Splinter, with different coauthors, [79–81] addressed feeding children varying liquids at different times before anesthesia and found no measurable effect on gastric fluid pH or volumes, but improved patient comfort. Also in 1990, Schreiner et al,[75] comparing children scheduled for outpatient surgery, allowed unlimited clear liquids up to 2 hours before induction of anesthesia in one group and noted no significant differences in gastric fluid pH or volume from a control group fasted 6 to 8 hours. Crawford et al[17] provided pediatric patients with water (2 mL/kg) and then fasted them for 2, 4, or 6 hours preoperatively. Again, neither gastric fluid volume nor pH were found to correlate with the duration of fast. Their conclusion was that children may be given water (2 mL/kg) up to 2 hours preoperatively without decreasing pH or increasing gastric fluid volume beyond values obtained after fasting for 6 hours. On the other hand, Meakin et al[51] have found that less than a 4-hour fasting period increased the volume of gastric aspirate compared with a control group, and they have criticized some of the other papers based on their small sampling size, concurrent use of H_2-receptors, and interpretation of data.[50]

The question is much different for children presenting for emergency surgery under general anesthesia. Bricker et al[7] stated that a "safe" interval between oral intake and induction of anesthesia could not be predicted, since 49% of children fasted greater than 8 hours had greater than 0.4 mL/kg gastric fluid volume, as did 31% who were injured more than 3 hours or longer after eating. Olsson and Hallen[59] noted that severity of trauma (e.g., small wound versus femoral fracture) was more important in gastric emptying than was fasting duration and concluded that no advantage could be gained by waiting for a "safe" interval to elapse between the last meal and anesthesia. Schurizek et al[76] observed that children between 6 and 10 years of age were at higher risk (i.e., pH < 2.5 and gastric fluid volume > 0.4 mL/kg) than younger age groups, and that a 4-hour fasting period before induction of anesthesia still resulted in over 50% of the children being at increased risk of aspiration.

With the exception of neonates, who do not tolerate prolonged fasting and fluid restriction, infants and children appear to tolerate 6-to 8-hour fasting without hypoglycemia.[8, 12, 42, 94]

PREOPERATIVE MEDICATION FOR CHILDREN

> We have not yet found either a suitable tranquilizing agent to help tolerate hospitalization or a satisfactory method of preanesthetic sedation. Instead, we continue to inject illogical doses of unpredictable agents.*
>
> ROBERT M. SMITH

The use of preoperative medications in pediatric anesthesia has always confronted the same issues facing the newspaper reporter: who, what, where, when, why, and how. Dealing with the small size and physiologic immaturity of the premature newborn, the rapid growth and development of the infant and young child, and the idiosyncratic mysteries of the adolescent, pediatric anesthesiologists have been reticent to put much faith in universal drug dosages or to expect identical results following the administration of even common medications. One has only to contrast the clinical situations of the critically ill neonate with congenital diaphragmatic hernia or coarctation of the aorta to that of the lusty cry of the appropriately resuscitated (and hungry!) 1-month-old infant with pyloric stenosis to appreciate that generalizations are difficult in pediatric cases and must be reassessed continually in terms of the specific patient population to whom one is providing anesthesia. Several general reviews concerning premedication administration[6, 46, 98] and a review of terminology[14] are available. The fine line between conscious sedation and actual induction of general anesthesia can be quite difficult to predict in the pediatric population. The principal factors encountered in this discussion include (1) dissatisfaction with the other premedications (e.g., the lytic cocktail or demerol-phenergan-thorazine injection),[78] (2) the development of newer agents and techniques for administering drugs to children,[62, 82] and (3) a belief that the premedication should be given with specific goals in mind and adapted to the individual patient. This is particularly true in the day-surgery setting.[18, 32] It must be emphasized that as each new agent and technique is developed, one must be cautious before randomly administering these premedications to children. The extremely rapid onset and potency of some of the newer agents,[19] the tendency to administer the drugs in locations without adequate monitoring, particularly in the younger age group,[55] and the ease of administration may lead those not familiar with the agents toward catastrophe.[36]

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*From Smith RM: The pediatric anesthetist, 1950–1975. Anesthesiology 43:144–155, 1975; with permission.

Narcotic Premedications

> Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficatious[sic] as opium.
>
> SYDENHAM, 1680

While the use of narcotics in pediatric anesthesia is discussed in another article in this issue, the significant role of old standbys and the newer agents as premedications is briefly addressed. Studies have shown that oral or parenteral narcotics, particularly when combined with other agents,[9, 25, 57] can be effective and acceptable in the outpatient setting. The use of an opiod premedication can result in lower endocrine stress responses[45] and, in addition, reduce the incidence of cardiac arrhythmias during halothane anesthesia in the pediatric population.[77] Children undergoing repetitive operations for burn debridement, orthopedic procedures, and congenital anomalies often seem to benefit from narcotic premedication, particularly if the postoperative course has been painful in the past, or if pain is anticipated before the induction of anesthesia (e.g., moving the child onto the operating room table). It should be emphasized that medications should be given early enough such that the premedicated state can be achieved before transporting the child from the room to the operating room, or it is unlikely that it will relieve the anxiety of the child or the accompanying family members. Our experience in pediatric anesthesia has been standard premedication orders (e.g., "on call to operating room or "at 10:15 AM") often do not work out well with busy operating room schedules due to case delays, overruns, and cancellations (more common in children associated with acute ear infections, upper respiratory infections, diarrhea, etc.). Stetson and Jessup[84] very vividly demonstrate the difficulty in timing a premedication for pediatric patients (Fig. 1). It is unfair to point the finger at a given drug as a therapeutic failure, when the circumstances surrounding the use of the agent condemn it to failure from the start.

Alternative Routes of Narcotic Administration

> "I'm allergic to needles. . . ."
>
> A YOUNG PATIENT

For the young child or an anxious teenager, the painful experience of an injection has often made the end hardly justify the means; likewise, the younger patient rarely associates the painful injection with analgesia at a later time. Recently, the addition of transoral and intranasal techniques[62, 82] for pediatric opioid administration, and the potential for transdermal possibilities in the future, may provide useful adjuncts for the management of pediatric patients (Table 1).

Several investigators[27, 56, 83] have demonstrated the effectiveness of buccal (transoral) absorption of fentanyl, thus avoiding problems with the portal circulation and first-pass, hepatic metabolism of the drug. Stanley et al[83] have shown that oral transmucosal fentanyl citrate (OTFC) in dosage of 15 to 20 μg/kg was readily accepted, significantly reduced anxiety, but did not greatly alter gastric fluid pH or volume compared with a placebo lollipop group. They did report a 50% incidence of mild preoperative pruritus, 44% incidence of postoperative nausea, and slower respiratory rates 10 minutes after administration. Friesen and Lockhart,[27] evaluating the use of droperidol for prevention of postoperative nausea following OTFC, noted

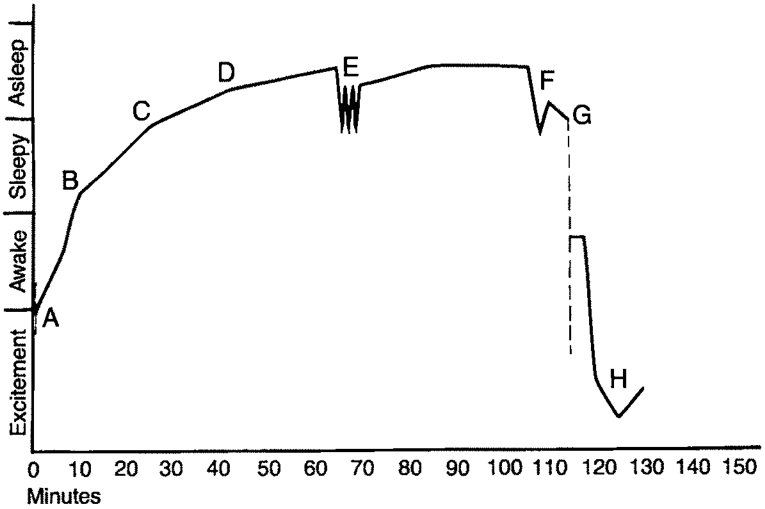

Figure 1. Premedication given at A was effective by C, with the child (aged 6 years 5 months weighing 47 lb) awakening with stimulation at E during transport to the operating room, but quickly returning to sleep. Unfortunately, the child's induction occurred at H, by which time the medication had become ineffective. Drug given orally: chloral hydrate, 790 mg; scopolamine, 0.69 mg. (*From* Stetson JB, Van Schaick G, Jessup BA: Use of oral chloral hydrate mixtures for pediatric premedication. Anesth Analg 41:208, 1962; with permission.)

hemoglobin desaturations below 90% in 12% of the OFTC group measured by pulse oximetry.

Intranasal sufentanil administration at a dose of 1.5 or 3.0 μg/kg was reported by Henderson et al[35] to facilitate parental separation, have minimal side effects, and provide some postoperative analgesia. However, they later cautioned that marked

Table 1. *Commonly Used Dosages and Routes of Administration of Pediatric Premedications*

MEDICATION	ROUTE OF ADMINISTRATION				
	Oral	*Intramuscular*	*Nasal*	*Rectal*	*Miscellaneous*
Morphine	0.1–0.4	0.1–0.2		0.1–0.2	
Fentanyl*					15–20 OTFC
Sufentanil* (Sufenta)			1.5–3.0		
Midazolam (Versed)	0.4–0.75	0.1–0.2	0.2–0.3	0.3	
Diazepam (Valium)	0.2	(NR)		0.5–0.75	
Pentobarbital (Nembutal)	2–4			3–5	
Methohexital (Brevital)				20–30	
Thiopental				30	
Chloral hydrate	30–50				
Ketamine	10	2–3	3		
Ranitidine (Zantac)	2.5	1–2			1.25 IV
Cimetidine (Tagemet)	7.5	7.5–10			
Metoclopramide	0.1	0.1			0.1 IV

All doses are milligram per kilogram except those with an asterisk, which are microgram per kilogram. Please read text for specific concerns with drugs. NR = not recommended.

ventilatory compliance decreases were observed when inhaled anesthetics were subsequently administered to the patients.[36] Jordan[38] presented alarming data, using 1.5 μg/kg nasal sufentanil, with all pediatric patients exhibiting respiratory depression and 45% having saturations below 88%. Ten percent of the patients required controlled ventilation 10 minutes after administration, and three patients required early muscle relaxants. This may be attributable to increased absorption resulting from the technique of administration. Helmers et al[34] demonstrated identical sufentanil plasma concentrations following IV or nasal administration at 30 to 120 minutes in adults.

Nonnarcotic Premedications: Benzodiazepines

Dissatisfaction with the postoperative emesis following narcotics, and the restlessness associated with chloral hydrate, has resulted in the increased use of a variety of benzodiazepines via oral, rectal, intranasal, and parenteral routes for premedication in children.[1, 49, 64, 67, 68, 71, 89, 95, 99] Recently, concern about the use of these agents, particularly with the addition of narcotics, resulting in respiratory depression and arrest has been noted.[3]

Midazolam (Versed), being water soluble and with a short elimination half-life, has enjoyed increasing popularity for day-surgery procedures, although it is not pleasant to receive orally or nasally. Oral administration of 0.5 mg/kg for children under 5 years, and 0.4 to 0.5 mg/kg for those over 5 years of age was recommended by Saarnivaara et al[67] using the parenteral form in a fruit juice. Anderson et al,[1] in Melbourne, administered 0.3 mg/kg orally, but noted that older children considered the medication in raspberry syrup unpalatable, and at that dose found it to offer no advantage over placebo. More recently Feld et al[23] reported that 0.5 to 0.75 mg/kg of midazolam orally provided effective preanesthetic sedation, but noted 9% to 17% of the children still were afraid or crying at induction 30 minutes later. Saint-Maurice et al[68] reported peak plasma concentrations 16 minutes after rectal administration (0.3 mg/kg in 5 mL of saline), which correlated with acceptable degree of sedation for mask inductions at 20 to 30 minutes following premedication. Intranasal administration of 0.2 or 0.3 mg/kg to preschool-aged children by Wilton et al[99] demonstrated acceptable sedation for mask induction at 10 minutes without changes in respiratory rate of oxyhemoglobin saturations, and no apnea during halothane induction. Taylor et al[89] noted satisfactory inhalational inductions following intramuscular administration of midazolam (0.2 mg/kg) in 78% of children at 30 to 60 minutes, with 25% having retrograde amnesia. Rita et al,[64] using 0.08 mg/kg intramuscularly, noted increasing sedation corresponded with increased age groups. Charlton et al,[11] studying intramuscular midazolam, 0.1 or 0.2 mg/kg, measured lower catecholamine concentrations during surgery following the higher dosage, and while noting slightly lower minute ventilation and respiratory rates, the ventilatory respose to carbon dioxide was adequate in both groups.

Oral diazepam (Valium) is frequently used for pediatric patients, although younger children (< 5 years) seem less sedated. Dosages from 0.25 to 0.5 mg/kg have been studied.[1, 95] Rectal administration has also been reported[49] using 0.4 to 0.5 mg/kg. Lorazepam, 0.05 mg/kg, has also been reported acceptable for children.[10]

Other Premedications

Chloral hydrate remains one of the standards of oral premedication; however, it is known for its bitter taste. Dose ranges from 30 to 50 mg/kg are commonly given. Trichlofos is no longer available.

The barbiturates have been used primarily for inducing sleep (hypnosis), but probably have little or no anxiolytic effect. They may be administered orally or rectally. Kestin et al[40] have demonstrated that the prolonged effects of rectally administered methohexital can be reduced by aspirating residual agent at the onset of sedation. Raftery and Warde[61] premedicated children with rectal thiopentone, 30 mg/kg, 30 minutes before induction and noted markedly reduced hypoxic incidents in children receiving isoflurane inductions. However, they also cited several borderline desaturations on arrival in the induction room. Larsson et al,[41] studying both rectal thiopentone (30 mg/kg) and methohexitone (20 or 30 mg/kg) in infants, observed elevated mean P_{CO_2} values and concluded that this age group is at increased risk of hypoventilation when associated with halothane anesthesia after premedication.

Ketamine, 2 mg/kg intramuscularly, is recommended for preinduction sedation of young children for outpatient procedures with a notably short onset time of about 3 minutes.[33] Oral administration, 10 mg/kg, is also reported to be advantageous for premedication in cardiac surgery patients.[86]

Droperidol has fallen from favor as a premedicant in pediatric patients following reported extrapyramidal hypertonic complications even at low doses.[20] However, Nicholson et al[58] administered the drug orally to 65 patients before strabismus surgery in an effort to minimize postoperative emesis, and noted a 50% reduction in the incidence of emesis with none of the patients demonstrating extrapyramidal tract signs.

The use of anticholinergic premedications can be helpful before the induction of anesthesia in young children. Friesen and Lichtor[26] have demonstrated the advantages of parenteral atropine in infants under 6 months of age to prevent bradycardia and hypotension during induction. Miller and Friesen[52] have subsequently demonstrated that oral atropine achieves the desired effect. Steward[85] recommends atropine (0.02 mg/kg) for prevention of oculocardiac reflex during eye surgeries, and Green et al[30] recommend the use of atropine (20 μg/kg) or glycopyrrolate (10 μg/kg) for prevention of bradycardia if repeated administration of suxamethonium is anticipated. The specific use of atropine in children with trisomy 21 has been studied by Wark et al[97] in Sydney where no cardioacceleratory problems were noted.

SUMMARY

The goal of safe, nonstressful, and anxiety-free induction of anesthesia for pediatric patients can be facilitated by minimizing the risks of aspiration pneumonitis and the conscientious use of an armamentarium of preoperative medications. The healthy child (ASA I or II) presenting for elective surgery, particularly in the day-surgery context, need not undertake a prolonged fast or be heavily premedicated before induction of anesthesia. Following a longer fasting period from solids, consumption of clear liquids up to 2 hours beforehand appears reasonable in view of the studies available. The variety of newer premedication agents and techniques should make it easier for the anesthesiologist to find an appropriate approach for the pediatric patient's specific needs. The potential for respiratory depression and apnea, particularly in infants and young children and in those with associated predisposing problems (e.g., large tongue, previous history of apnea, etc.) must remain a primary consideration in drug administration. Once again, the choice of premedications must be focused on the old axiom: who, what, where, when, why, and how.

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Opioids in Pediatric Anesthesia and in the Management of Childhood Pain

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The treatment and alleviation of pain is a basic human right that exists regardless of age. Unfortunately, even when their pain is obvious, children are rarely treated for pain or for painful procedures.[13–15, 95, 110, 112] This has been particularly true for the newborn.[3, 4, 123, 141] Indeed, what other patient population has surgical (e.g., circumcision) or medical (e.g., mechanical ventilation and paralysis without sedation) procedures routinely performed without the benefits of anesthesia or analgesia?[95, 100, 141] The common "wisdom" that children neither respond to, nor remember, painful experiences to the same degree that adults do is simply not true.[1, 4, 13, 15, 72, 79, 95, 101]

Unfortunately, even when physicians decide to treat children who are in pain, they rarely prescribe potent analgesics or adequate doses, because of their concern that children may be harmed by the use of these drugs.[10, 75, 110, 111, 114, 144] This is not at all surprising because physicians and nurses are taught throughout their training that opiates cause respiratory depression, cardiovascular collapse, depressed levels of consciousness, vomiting, and, with repeated use, addiction.[20, 26, 75, 78, 80, 81, 103, 130] Rarely, if ever, are the appropriate therapeutic uses of opioids, or rational dosing regimens, discussed.

As anesthesiologists, we have a special role in the treatment of both acute and chronic pain and in the education of our colleagues in the use of opioids because of our specialized knowledge and skills in using them. The purpose of this review is to highlight some of the advances in opioid pharmacology and in therapeutic interventions, both in and out of the operating room, that have occurred over the past decade. Specifically, we (1) delineate the role of opioid receptors in the mechanism of opioid analgesia, (2) provide a pharmacokinetic and pharmacodynamic framework regarding the use of opioids in children, (3) describe the use (and limitations) of fentanyl as a "complete" single anesthetic agent in the newborn, and (4) provide guidelines for pain management using patient-controlled analgesia, methadone, and spinally administered opiates.

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OPIOID RECEPTORS

Over the past 20 years multiple opioid receptors and subtypes have been identified and classified (Table 1).[34, 53, 68, 76, 83, 96, 118, 122, 132, 133] Understanding the complex nature and organization of these multiple opioid receptors is essential in order to adequately respond to and control pain. In the central nervous system (CNS) there are four opioid receptor types, designated mu (for morphine), kappa, delta, and sigma. The mu receptor is further subdivided into mu$_1$ (supraspinal analgesia) and mu$_2$ (respiratory depression, inhibition of gastrointestinal motility) subtypes.

Organizationally, the distribution of the multiple opioid receptors may have significance in the modulation of pain (Table 1). Nociceptive impulses are transmitted from the periphery to the dorsal horn of the spinal cord where diverse synapses occur with essentially all incoming sensory input.[8, 30, 71, 82, 99] In the substantia gelatinosa of the dorsal horn of the spinal cord, interneurons are activated and release substance P, an 11-amino acid peptide pain transmitter that facilitates nociceptive transmission.[8, 44, 99, 126] Descending fibers also synapse at the interneurons to inhibit or modulate sensory input about an injury as well, via the release of endogenous opioids and other neuropeptides.[24, 83, 118, 126] If unblocked, nociceptive input is transmitted to the brain via the spinothalamic and spinoreticular nerve pathways.[8, 131] Several areas within the brain may further modulate or abolish pain transmission including the brainstem's medial and lateral reticular formations, the medullary raphe nuclei, the periaqueductal grey, the thalamus, and the cerebral cortex. Binding of either endogenous or pharmacologically administered opiates to receptors in these central locations initiates the modulation of pain transmission. Thus, the organization of opioid systems suggests that there may be a multiplicity of sites at which opioids might modify nociception.

The differentiation of agonists and antagonists is fundamental to pharmacology. A neurotransmitter is defined as having agonist activity, while a drug that blocks the action of a neurotransmitter is an antagonist.[22, 53, 83, 99, 118, 132, 133] By definition, receptor recognition of an agonist is "translated" into other cellular alterations (i.e., the agonist initiates a pharmacologic effect), whereas an antagonist occupies the receptor without initiating the transduction step (it has no intrinsic activity or efficacy). The intrinsic activity of a drug defines the ability of the drug-receptor

Table 1. *Classification of Opioid Receptors*

RECEPTOR	PROTOTYPE AGONIST	CNS LOCATION	EFFECTS
mu	Morphine Fentanyl Meperidine Codeine Methadone	Brain: laminae III and IV of the cortex, thalamus periaqueductal grey Spinal cord: substantia gelatinosa	mu$_1$ supraspinal analgesia, dependence mu$_2$ respiratory depression, inhibition of gastrointestinal mobility, bradycardia
kappa	Ketocyclazocine Dynorphin Butorphanol?	Brain: hypothalamus, periaqueductal grey, claustrum Spinal cord: substantia gelatinosa	Spinal analgesia, sedation, miosis, inhibition of antidiuretic hormone release
delta	Enkephalins DADL	Brain: pontine nucleus, amygdala, olfactory bulbs, deep cortex	Analgesia, euphoria
sigma	N-allylnormetazocine Phencyclidine Ketamine?		Dysphoria, hallucinations

complex to initiate a pharmacologic effect. Drugs that produce less than a maximal response have a lowered intrinsic activity and are called partial agonists. Partial agonists also have antagonistic properties, because by binding the receptor site, they block access of full agonists to the receptor site. Morphine and related opiates are mu agonists, and drugs that block the effects of opiates at the mu receptor, such as naloxone, are designated antagonists. The opioids most commonly used in anesthetic practice and in the management of pain are mu agonists (Table 2). These include morphine, meperidine, methadone, and the fentanyls. Mixed agonist-antagonist drugs act as agonists or partial agonists at one receptor and antagonists at another receptor. Mixed (opioid) agonist-antagonist drugs include pentazocine, butorphanol, nalorphine, and nalbuphine.[104, 106] Most of these drugs are agonists or partial agonists at the kappa and sigma receptors and antagonists at the mu receptor (Table 3).

The mu receptor and its subspecies and the delta receptor produce analgesia, respiratory depression, euphoria, and physical dependence. Morphine is 50 to 100 times weaker at the delta than at the mu receptor. By contrast, the endogenous opiate-like neurotransmitter peptides known as the enkephalins tend to be more

Table 2. *Commonly Used mu Agonist Drugs*

AGONIST	EQUIPOTENT IV DOSE (mg/kg)	DURATION (h)	ORAL BIOAVAILABILITY (%)	COMMENTS
Morphine	0.1	3–4	20–40	Seizures in newborns; also in all patients at high doses Histamine release, vasodilation →→ avoid in asthmatics and in circulatory compromise MS-contin, 8–12 h duration
Meperidine	1.0	3–4	40–60	Catastrophic interactions with monoamine oxidase inhibitors Tachycardia; negative inotrope Metabolite produces seizures; not recommended for chronic use
Methadone	0.1	4–24	70–100	Can be given IV even though the package insert says subcutaneously or intramuscularly
Fentanyl	0.001	0.5–1		Bradycardia; minimal hemodynamic alterations Chest wall rigidity (>5 µg/kg rapid IV bolus). Prescribe naloxone or succinylcholine or pancuronium
Codeine	1.2	3–4	40–70	Orally only Prescribe with acetaminophen

Table 3. *Action of Opioids at Receptor Subtypes*

	RECEPTOR SUBTYPE		
DRUG	*Mu*	*Kappa*	*Sigma*
Morphine	Agonist	Agonist	
Naloxone	Antagonist	Antagonist	Antagonist
Naltrexone	Antagonist		
Pentazocine	Antagonist	Agonist	Agonist
Butorphanol		Agonist	Agonist
Nalbuphine	Antagonist	Partial agonist	Agonist

potent at delta and kappa than at mu receptors. The kappa receptor, located primarily in the spinal cord, produces spinal analgesia, miosis, and sedation with minimal associated respiratory depression. The sigma receptor is responsible for the psychotomimetic effects observed with some opiate drugs, particularly the mixed agonist-antagonist drugs. These effects include dysphoria and hallucinations.

A number of studies suggest that the respiratory depression and analgesia produced by mu agonists involve different receptor subtypes. These receptors change in number in an age-related fashion and can be blocked by naloxone. Pasternak et al,[97, 151] working with newborn rats, showed that 14-day-old rats are 40 times more sensitive to morphine analgesia than 2-day-old rats. Nevertheless, morphine depresses the respiratory rate in 2-day-old rats to a greater degree than in 14-day-old rats. Thus, the newborn may be particularly sensitive to the respiratory depressant effects of the commonly administered opioids in what may be an age-related receptor phenomenon. This has important clinical implications for the use of narcotics in the newborn.

PHARMACOKINETICS

To relieve or prevent pain, the agonist must get to the receptor in the CNS. There are essentially two ways that this occurs, either via the blood stream (following intravenous [IV], intramuscular, oral, nasal, transdermal, or mucosal administration) or by direct application (intrathecal or epidural) into the cerebrospinal fluid (CSF).[21, 22, 135–139] Agonists administered via the blood stream must cross the blood-brain barrier, a lipid membrane interface between the endothelial cells of the brain vasculature and the extracellular fluid of the brain, to reach the receptor. Normally, highly lipid-soluble agonists, such as fentanyl, rapidly diffuse across the blood-brain barrier, whereas agonists with limited lipid solubility, such as morphine, have limited brain uptake. The blood-brain barrier may be immature at birth and is known to be more permeable to morphine. Indeed, Way et al[61, 128] demonstrated that morphine concentrations were two to four times greater in the brains of younger rats than older rats despite equal blood concentrations.

Spinal administration, either intrathecally or epidurally, bypasses the blood and directly places an agonist into the CSF, which bathes the receptor sites in the spinal cord (substantia gelatinosa) and brain. This "back door" to the receptor significantly reduces the amount of agonist needed to relieve pain. After spinal administration, opioids are absorbed by the epidural veins and redistributed to the systemic circulation where they are metabolized and excreted. Hydrophilic agents, such as morphine, cross the dura more slowly than more lipid soluble agents such as fentanyl or meperidine. This physicochemical property is responsible for the more prolonged duration of action of spinal morphine and its very slow onset of action after epidural administration.[23, 35, 37]

Although it would be desirable to adjust opioid dosage based on the concentration of drug achieved at the receptor site, this is rarely feasible. The alternative is to measure blood or plasma concentrations and model how the body handles a drug. Pharmacokinetic studies thereby help the clinician select suitable routes, timing, and dosing of drugs to maximize a drug's dynamic effects.

Following administration, the disposition of a drug is dependent on distribution ($t_{1/2}\alpha$) and elimination. The terminal half-life of elimination ($t_{1/2}\beta$) is directly proportional to the volume of distribution (Vd) and inversely proportional to the total body clearance (Cl) by the following formula:

$$t_{1/2}\beta = 0.693 \times (Vd/Cl)$$

Thus, a prolongation of the $t_{1/2}\beta$ may be due to either an increase in a drug's volume of distribution or by a decrease in its clearance.

Morphine, meperidine, methadone, and fentanyl are biotransformed in the liver before excretion.[53, 132] Many of these reactions are catalyzed in the liver by microsomal mixed-function oxidases that require the cytochrome P-450 system, NADPH, and oxygen. The cytochrome P-450 system is very immature at birth and does not reach adult levels until the first month or two of life. The immaturity of this hepatic enzyme system may explain the prolonged clearance or elimination of some opioids in the first few days to weeks of life (see following). On the other hand, the P-450 system can be induced by various drugs (phenobarbital) and substrates and matures regardless of gestational age. Thus, it is the age from birth, and not the duration of gestation, that determines how premature and full-term infants metabolize drugs. Indeed, Greeley and de Bruijn[42] have demonstrated that sufentanil is more rapidly metabolized and eliminated in 2- to 3-week-old infants than newborns less than a week postnatal age.

Morphine and fentanyl are primarily glucuronidated into inactive forms that are excreted by the kidney, whereas approximately one third of meperidine is demethylated into normeperidine, a metabolite that is half as active as meperidine as an analgesic but twice as active as a convulsant. Because of this potential risk of seizures, we believe that meperidine should not be prescribed for chronic pain management.

Fentanyl is highly lipid soluble and is rapidly distributed to tissues that are well perfused, such as the brain and the heart.[19, 47, 52, 77, 116] Normally, the effect of a single dose of fentanyl is terminated by rapid redistribution, rather than by elimination, in a manner similar to thiopental. However, following multiple or large doses of fentanyl (e.g., when it is used as a primary anesthetic agent), prolongation of effect will occur, because elimination and not distribution will determine the duration of effect (see following). This is particularly important in the newborn, in whom elimination may be further prolonged by abnormal or decreased liver blood flow following acute illness or abdominal surgery.[33, 46, 55] Additionally, increases in intraabdominal pressure may further decrease liver blood flow by shunting blood by the liver via a patent ductus venosus (see following).

The pharmacokinetics of morphine and fentanyl have been extensively studied in adults, older children, and in the premature and full-term newborn.[16, 56, 57, 69, 70] Following an IV bolus, 30% of morphine is protein bound in the adult versus only 20% in the newborn. This increase in unbound ("free") morphine allows a greater proportion of the drug to penetrate the brain. This may explain, in part, the observation of Way et al[61, 128] of increased brain levels of morphine in the newborn and its more profound respiratory depressant effects. The elimination half-life of morphine in adults and older children is 3 to 4 hours and is consistent with its duration of analgesic action (Table 4).[61, 128] The $t_{1/2}\beta$ is more than twice as long in

Table 4. *Morphine Pharmacokinetics*

	PREMATURE (<33 wk)	FULL TERM	ADULT
$t_{1/2}\beta$	7.4 ± 1.7	6.7 ± 4.6	3.0
Clearance (mL/kg/min)	9.6 ± 4.0	15.5 ± 10.0	3.2
Vd (L/kg)	5.18 ± 1.6	2.9 ± 2.1	15

newborns less than a week of age than in older children and adults and is even longer in premature infants. Clearance is similarly decreased in the newborn compared with the older child and adult (Table 4). Thus, the serum concentration of morphine is greater in newborns than in older children and will decline more slowly than it will in older children and adults. This may also account for the increased respiratory depression associated with morphine in the newborn group.

Interestingly, the half-life of elimination and clearance of morphine in infants older than 2 months of age is similar to adult values. Thus, the hesitancy in prescribing and administering morphine to infants 2 to 12 months of age may not be justified on the basis of altered pharmocokinetics. On the other hand, the use of any opioid in children less than 2 months of age must be limited to a monitored, intensive care unit setting.

Based on its relatively short half-life (3–4 h), one would expect older children and adults to require supplemental doses of morphine every 2 to 3 hours, particularly if the morphine is administered by IV (Fig. 1).[114, 145] This has led to the recent use of continuous infusion regimens of morphine and patient-controlled analgesia (PCA) (see following), which maximize pain-free periods. Alternatively, longer-acting agonists such as methadone may be used.[10, 11, 36, 39–41, 102, 114] Methadone is metabolized extremely slowly in children and has a very prolonged duration of action. The $t_{1/2}\beta$ of methadone averages 19 hours and clearance averages 5.4 $mL \cdot min^{-1} \cdot kg^{-1}$.

Finally only about 30% of an orally administered dose of morphine reaches the systemic circulation.[36, 38, 75, 90] When converting from an IV morphine requirement to the oral equivalent, the dose required is three to four times greater than the IV dose. Oral morphine is available as a liquid, tablet, and sustained-release preparation (MS-contin).

Fentanyl and its structurally related relatives, sufentanil and alfentanil, are highly lipophilic drugs that rapidly penetrate all membranes including the blood-brain barrier. Following an IV bolus, fentanyl is rapidly eliminated from plasma as the result of its extensive uptake by body tissues. In blood, the fentanyls are highly bound to $alpha_1$ acid glycoprotein. This protein is present in low concentrations in newborn blood. The fraction of free unbound sufentanil in neonates and children less than a year of age (19.5 ± 2.7% and 11.5 ± 3.2%, respectively) is significantly greater than that in older children and adults (8.1 ± 1.4% and 7.8 ± 1.5%, respectively). This difference correlates with age-related differences in the concentration of $alpha_1$ acid glycoproteins in the blood.

Fentanyl pharmacokinetics differ between newborn infants, children, and adults. The total body clearance of fentanyl in infants 3 to 12 months of age is greater than it is in children older than 1 year of age or in adults (18.1 ± 1.4, 11.5 ± 4.2, and 10.0 ± 1.7 $mL \cdot kg^{-1} \cdot min^{-1}$, respectively) and the half-life of elimination is longer (233 ± 137, 244 ± 79, and 129 ± 42 min, respectively).[33, 46, 116, 117] The prolonged elimination half-life of fentanyl from plasma has important clinical implications. If repeated doses of fentanyl were given too frequently for maintenance of analgesia, fentanyl could accumulate and depress ventilation.[19, 47, 55, 77] Very large doses (0.05–0.10 $mg \cdot kg^{-1}$, as used in anesthesia) may be expected to induce long-lasting effects because plasma fentanyl levels could remain above the

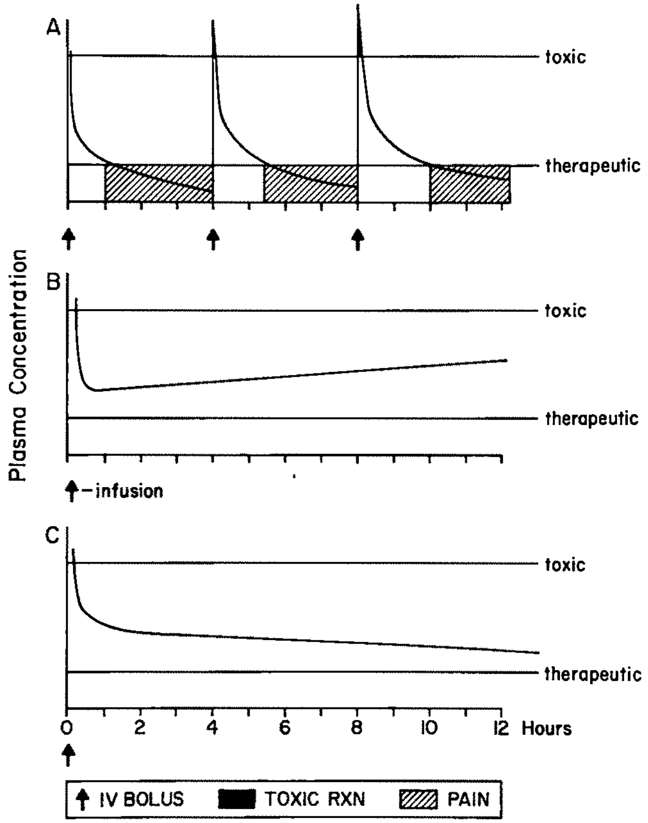

Figure 1. Simulated blood concentration-dose relationships for opioids by different administration regimens. (*A*) Intravenous bolus administration of morphine sulfate (elimination half-life, 4 hours) every 4 hours. (*B*) Intravenous bolus administration of morphine sulfate followed by a continuous intravenous infusion. (*C*) Intravenous bolus administration of methadone (elimination half-life, 19 hours). Note the absence of pain periods in dosing regimens *B* and *C*. (*From* Yaster M, Deshpande JK, Maxwell LG: The pharmacologic management of pain in children. Compr Ther 15:14–26, 1989; with permission.)

threshold level at which spontaneous ventilation occurs during the distribution phases. On the other hand, infants greater than 3 months of age may tolerate more drug without respiratory depression since the greater clearance of fentanyl will lower the plasma concentrations.[46, 116]

NARCOTIC ANESTHESIA FOR NEWBORN SURGERY

In the past, many newborns were paralyzed rather than anesthetized for surgery because of concerns of excessive hypotension.[31, 87, 127] In a landmark paper, Robinson and Gregory[108] reported the first use of fentanyl, 30 to 50 μg/kg, as the principal anesthetic agent in neonates undergoing ductus ligation surgery. Using heart rate and blood pressure responses as an index of adequate anesthesia, these investigators demonstrated that the combination of fentanyl, oxygen, and pancu-

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ronium could provide anesthesia with minimal hemodynamic consequences. Indeed, the hemodynamic stability associated with fentanyl (and sufentanil) administration in the newborn has been confirmed by several other investigators.[42, 48–50, 55, 142] In all reported studies, both hypotension and bradycardia are rare, as long as a vagolytic agent (either pancuronium or atropine) is administered concomitantly. Furthermore, in a newborn lamb model, we demonstrated that fentanyl did not significantly affect heart rate, blood pressure, cardiac output, or the regional distribution of blood flow to the major organs, such as the brain and gastrointestinal tract, when it was administered in doses ranging between 30 and 3000 μg/kg.[146] On the other hand, the safety of "fentanyl" anesthesia may be compromised, when other anesthetic agents, such as nitrous oxide, barbiturates, or benzodiazepines are administered concomitantly.[147]

Yaster extended the observations of Robinson and Gregory in a prospective study of premature and full-term newborns less than 7 days of age undergoing a variety of thoracic, abdominal, and genitourinary emergency operations.[142] In this study, fentanyl in doses of 10 to 12.5 μg/kg produced insignificant hemodynamic changes and provided reliable anesthesia for at least 75 minutes. There are several reasons for the discrepancies in fentanyl requirements in these studies. Robinson and Gregory studied premature infants ranging in age from 1 day to 6 weeks undergoing thoracic surgery,[108] whereas Yaster studied younger infants (the majority were < 24 hours old). Analgesic requirements are reduced in the first few days of life.[1, 3, 28, 63, 64] This may be attributed to the presence of endogenous opioids that were stimulated by birth or fetal and neonatal distress. As mentioned earlier, the blood-brain barrier is immature in the first few days of life, and this may allow more fentanyl to reach the mu receptors within the CNS. However, this is more important for less lipid soluble agonists such as morphine.[61, 128] Alternatively, the increased fraction of free, unbound fentanyl in the newborn may allow more drug to penetrate the brain. In addition, fentanyl clearance increases dramatically in the first weeks of life, probably as a result of increasing activity of the cytochrome P-450 system and increasing hepatic blood flow following closure of the ductus venosus.[55] Thus, the increased fentanyl metabolism that occurs in older newborns may increase their anesthetic (fentanyl) requirements. Finally, many of the infants in the study by Yaster underwent abdominal surgery or had significant abdominal pathology such as necrotizing enterocolitis. Fentanyl clearance as well as analgesic requirements may be significantly decreased in these situations, particularly if intraabdominal pressure increases. Increased intraabdominal pressure (>15–20 mm Hg) markedly reduces liver and splanchnic blood flow and this effect has been documented following closure of abdominal wall defects such as omphalocele or gastroschisis.[55, 143, 149] This decreased liver blood flow reduces fentanyl biotransformation and thereby anesthetic requirements. The dose of fentanyl in newborns may therefore depend on the postnatal age, the type of surgery, and the patient risk factors including acidosis, hypoxia, and circulatory stability.

The need to provide anesthesia rather than paralysis is also abundantly clear.[4, 5, 141] Trauma, whether iatrogenic (surgery) or accidental, is known to release stress hormones (catecholamines, corticosteroids, growth hormone, and glucagon).[54, 150] These stimulate a cascade of catabolic changes that lead to a breakdown of protein, glycogen, and fat stores. Although initially important in maintaining circulatory homeostasis, these processes may prevent wound healing and compromise both humoral and cellular immunity. Anand et al[1–5, 101] demonstrated that the newborn responds to surgical stress by suppressing insulin secretion and by releasing more catecolamines, glucagon, and corticosteroids than adult patients would. These hormonal changes precipitate hyperglycemia, lactic acidosis, and protein breakdown. Fentanyl (10 μg/kg) and nitrous oxide together attenuate these responses. In one study, Anand et al[5] noted an increased incidence of postoperative complications including intraventricular hemorrhage in infants anesthetized with N_2O-curare compared with the same anesthetic with fentanyl (10 μg/kg). The use of high-dose sufentanil intraoperatively and postoperatively to provide aggressive anesthesia and analgesia in complex congenital heart disease repair has also been shown in preliminary studies by Anand et al to significantly affect postoperative mortality.[6]

PREINDUCTION OF ANESTHESIA AND PREMEDICATION

Fear of painful and unpleasant procedures, separation from parents, and an unwillingness to breathe through an anesthesia face mask may produce stormy anesthetic inductions in unpremedicated children. Because of this, preanesthetic sedation has become an integral part of pediatric anesthetic practice. A variety of medications administered at various times and by various routes (oral, nasal, intramuscular, transmucosal, and rectal) have been used for this purpose.[12, 17, 18, 45, 65–67, 88–89, 105, 107, 119, 120] Unfortunately, each drug and administration technique has some disadvantage. A search for a drug and method of delivery that enhances the anesthesiologist's ability to induce anesthesia effectively and atraumatically remains elusive.

Henderson et al[45] have recently introduced the concept of "preinduction of anesthesia" with nasally administered sufentanil. "Preinduction of anesthesia induces a state of consciousness different from that produced by pre-medicants administered orally or intramuscularly. In this technique, children become relaxed, occasionally euphoric, and usually calm and cooperative. It differs from pre-medicants such as rectally administered methohexital in that it does not produce drowsiness or sleep."[45] The high lipid solubility of the fentanyls, particularly sufentanil, allows for rapid absorption of this family of drugs across the nasal mucosa. Although some believe that the nasal administration of sufentanil is less traumatic than either an intramuscular or IV injection, 61% of the children in their study found that nasally administered sufentanil was unpleasant and cried during its application.[45] Sufentanil is effective when nasally administered in doses of 1.5 to 3.0 μg/kg. Higher doses (4.5 μg/kg) produce untoward side effects including chest wall rigidity, convulsions, respiratory depression, and increased postoperative vomiting.[45]

Another exciting alternative to IV or intramuscular injection is the fentanyl lollipop or "oral transmucosal fentanyl citrate."[29, 85, 119–121] In doses of 15 to 20 μg/kg, this is an effective, nontraumatic method of premedication that is self-administered and extremely well accepted by children. Side effects include facial pruritus (90%), slow onset time (25–45 minutes to peak effect), and an increase in gastric fluid volume compared with that in unpremedicated patients (15.9 ± 10.8 mL compared with 9.0 ± 6.2 mL, mean ± SD).[120, 121] The increase in gastric contents is probably of no clinical significance, since aspiration has never been reported with this technique. Unfortunately, oral transmucosal fentanyl citrate may never reach the marketplace or receive Food and Drug Administration approval as a result of concerns that tainting candy with opioids sends the wrong message to children.

PATIENT-CONTROLLED ANALGESIA

Because of the enormous individual variations in pain perception and opioid metabolism, fixed ("Harriet Lane") doses and time intervals make little sense. Based on the pharmacokinetics of the opioids, it should be clear that IV boluses of morphine or meperidine may need to be given at intervals of 1 to 2 hours in order to avoid marked fluctuations in plasma drug levels (Fig. 1).[10, 73, 75, 114, 145] Continuous IV infusions can provide steady analgesic levels and are preferable to intramuscular injections but are not a panacea because the perception and intensity of pain is not constant. Indeed, the most common method of opioid administration in adults and children is intramuscular injection. It is well known that children will suffer in silence and underreport their level of pain, rather than ask for yet another painful injection.[10, 13, 26, 75, 81, 90, 95, 114, 144] Thus, rational pain management requires some form of titration to effect whenever an opioid is administered. In order to give patients some measure of control over their pain therapy, demand analgesia or PCA devices have been developed.[32, 51, 109, 113, 124, 129] These are microprocessor driven pumps with a button that the patient presses to self-administer a small dose of opioid. This treatment modality may be particularly suitable for the adolescent age group and patients with sickle cell anemia who present in vasoocclusive crises.[115]

Demand analgesia devices allow patients to administer small amounts of an analgesic whenever they feel a need for more pain relief. The opioid, usually morphine, is administered either IV or subcutaneously. The dose of opioid, number of boluses per hour, and the time interval between boluses (the "lock-out period") are programmed into the equipment by the pain service physician to allow maximum patient flexibility and sense of control with minimal risk of overdose.[74, 91–94] Generally, because patients know that if they have severe pain they can obtain relief immediately, most prefer dosing regimens that result in mild-to-moderate pain in exchange for fewer side effects such as nausea. Typically, we initially prescribe morphine, 20 μg/kg per bolus, at a rate of 6 boluses per hour, with an 8 minute lock-out interval between each bolus. Some administer larger boluses (30–50 μg/kg) over shorter time intervals (5 minutes). The computer within the PCA pump has memory capabilities to count the number of boluses a patient has received as well as the number of attempts to trigger boluses. This allows the physician to evaluate how well the patient understands the use of the pump and provides information to program the pump more efficiently. Many PCA units use low "background" continuous infusions (morphine, 20 to 30 μg/kg/h) in addition to self-administered boluses. This is sometimes called "PCA plus."

PCA requires a patient with enough intelligence and manual dexterity and strength to operate the pump. Thus, it was initially limited to adults, adolescents, and teenagers, but the lower age limit has decreased. In fact, it has been our experience that any child who is proficient at Nintendo can operate a PCA pump. Extensive studies in adult patients reveal that patients are extremely satisfied with this mode of therapy. Difficulties with PCA include its increased costs, patient age limitations, and the bureaucratic (physician, nursing, and pharmacy) obstacles (protocols, education, storage arrangements) that must be overcome before its implementation. Contraindications to PCA pumps include inability to push the bolus button (weakness, arm restraints), inability to understand how to use the machine, and a patient's desire not to assume responsibility for his or her own analgesia.

METHADONE

Primarily thought of as a drug to treat or wean patients who were addicted to or dependent on opioids, methadone is increasingly being used for postoperative pain relief and for the treatment of intractable pain.[10, 11, 36, 39–41, 102, 114] Methadone is noted for its slow elimination, very long duration of effective analgesia, and high oral bioavailability (see Table 2). Methadone has the longest $t_{1/2}\beta$ of any of the commonly available opiates and may provide 12 to 36 hours of analgesia following a single IV dose.[36, 39–41, 102] Pharmacokinetically, the effects of methadone in children are indistinguishable from those in young adults. The $t_{1/2}\beta$ of methadone averages 19.2 hours, and the clearance averages 5.4 $\text{mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ in children 1 to 18 years of age.[11] Because a single dose of methadone can achieve and sustain a high drug plasma level, it is a convenient way to provide prolonged analgesia without requiring an intramuscular injection (see Fig. 1).[145] Indeed, when administered either orally or IV, it may be viewed as an alternative to the use of continuous IV opioid infusions (a "poor man's" PCA). Berde[10] recommends administration of a loading dose of IV methadone, 0.1 to 0.2 mg/kg^{-1}, and then titrating in 0.05 mg/kg^{-1} increments every 10 to 15 minutes until an adequate level of analgesia is achieved. Supplemental methadone can be administered in 0.05 to 0.1 mg/kg^{-1} increments administered by slow IV infusion every 4 to 12 hours as needed. Berde[10] has also reported the use of small incremental doses administered by "sliding scale." "Small increments of methadone are administered intravenously over 20 minutes every 4 hours via a 'sliding' scale on a 'reverse prn' (the nurse asks the patient) basis: 0.07 to 0.08 mg/kg for severe pain; 0.05 to 0.06 mg/kg for moderate pain; 0.03 mg/kg for little or no pain, if the patient is alert; and no drug if the patient has little pain and is somnolent."[10] The influence of pathophysiology on the pharmacokinetics and pharmacodynamics of methadone are unknown primarily because its use as an analgesic is a relatively recent phenomenon. Dosing decisions in the very young and in patients with various end-organ diseases must be made conservatively. Finally, because methadone is extremely well absorbed from the gastrointestinal tract and has a bioavailability of 80% to 90%, it is extremely easy to convert from IV to oral dosing regimens.

INTRATHECAL AND EPIDURAL OPIOID ANALGESIA

The presence of high concentrations of opioid receptors in the spinal cord makes it possible to achieve analgesia, in both acute and chronic pain, with small doses of opioids administered in either the subarachnoid or epidural spaces.[23, 138, 139, 134–136] By bypassing the blood and the blood-brain barrier, small doses of opioids are effective because they can reach the receptor by the "back-door." Indeed, opioid levels in the CSF, particularly for morphine, are several thousand times greater than those achieved by the parenteral route (see following).[43, 86] It is these high levels that produce the profound and prolonged analgesia that accompanies intrathecal and epidural opioid administration.

Yaksh and Rudy[140] demonstrated, in unanesthetized rats, that intrathecal narcotics produced profound segmental analgesia that is dose dependent and reversible with naloxone. However, after 1 hour, rostral spread was evident, especially at higher doses.[140] The passage of epidurally administered agonists across the dura into the CSF depends on the lipid solubility of the drug. Additionally, once in the CSF, opioids must pass from the water phase of the CSF into the lipid phase of the underlying neuraxis to reach the receptor. This too is dependent on lipid solubility. Hydrophilic agents such as morphine will have a greater latency and duration of action than more lipid soluble agents such as fentanyl.[37] On the other hand, the lipid-soluble agonists produce more segmental analgesia with less rostral spread than the less lipid-soluble agonists.[35]

Even when administered via the caudal route, epidural morphine has been shown to provide effective postoperative analgesia following abdominal, thoracic, and cardiac surgery.[25, 59, 60, 125, 148] Krane et al[60] recently reported that 0.03 mg/kg of caudal-epidural morphine is equally effective as 0.1 mg/kg in providing postoperative analgesia, although the higher dose provides a significantly longer duration of analgesia (13.3 ± 4.7 versus 10.0 ± 3.3 hours, respectively). The incidence of side effects was the same in both groups, although one patient who received 0.1 mg/kg developed late respiratory depression. Therefore, these investigators suggest starting with the lower dose of morphine when using this technique. We routinely administer intrathecal morphine intraoperatively to children undergoing craniofacial procedures, particularly when a lumbar CSF drain is placed as a method of intraoperative brain decompression management.[86] We find that it provides excellent intraoperative and postoperative trigeminal nerve analgesia with minimal side effects (see following).

Spinal opiates produce analgesia without altering autonomic or neuromuscular function. Additionally, both light touch and proprioception are preserved. Thus, unlike local anesthetics, spinal opioids allow patients to ambulate without orthostatic hypotension. Common side effects of intrathecal and epidural narcotics include facial or segmental pruritus, urinary retention, nausea and vomiting, and respiratory depression.[7, 9, 27, 62, 84, 98] These side effects occur with greater frequency when opioids are administered intrathecally as opposed to epidurally. Except for urinary retention, reversal of adverse side effects, with maintenance of adequate analgesia, can be achieved through the use of a low dose (0.001–0.002 mg • kg^{-1} • h^{-1}) naloxone infusion. Pruritus and nausea can also be treated with IV diphenhydramine (Benadryl), 0.5 to 1.0 mg/kg. Urinary retention has not been a reported complication in children because in the pediatric population studied to date, all patients have had bladder catheters as part of their postoperative management regimen.

Although rare, respiratory depression is a major risk when using intrathecal and epidural opioids.[7, 9, 27, 62, 84, 98] Attia et al[7] demonstrated that the ventilatory response to CO_2 is depressed for as long as 22 hours after administration of 0.05 mg/kg^{-1} of morphine epidurally. Nichols et al[86] demonstrated significant depression of the ventilatory response to carbon dioxide for up to 18 hours after administration of intrathecal morphine (0.02 mg/kg) in children 3 months to 15 years of age. The greatest respiratory depression correlated with the highest CSF morphine levels (2863 ± 542 ng/mL), which occurred 6 hours after administration. This depression persisted despite a decrease in CSF morphine levels 12 (641 ± 219 ng/mL) to 18 (223 ± 152 ng/mL) hours later. This confirms the clinical impression that respiratory depression usually occurs within the first 6 hours after the administration of epidural or intrathecal morphine but may also occur as a late (up to 18 hours) complication.

In clinical practice, respiratory depression after intrathecal opioid occurs when IV or intramuscular narcotics have been administered to supplement the intrathecal opioid. The risk of respiratory depression can be minimized by avoiding supplemental parenteral narcotics or by using shorter acting, more lipid-soluble opioids (fentanyl, sufentanil) in the intrathecal space. The latter opioids provide more segmental analgesia, with less rostral spread. On the other hand, because of their shorter duration of action, fentanyl and sufentanil are increasingly being administered by continuous epidural infusion, either alone or in combination with very dilute (1/16%, 0.0625 mg/mL) bupivacaine concentrations. Typically, the epidural solution contains 1 to 2 μg/mL of fentanyl, with or without bupivacaine, and is administered at rates ranging between 0.2 and 1.0 mL/kg/h. This provides effective analgesia for both postoperative and chronic cancer pain. Sufentanil (0.75 μg/kg), the only drug approved for epidural use by the Food and Drug Administration, has been shown to provide effective analgesia in children ranging between 4 and 12 years for about 2 hours.

Regardless of the opioid and route of administration, routine monitoring for respiratory depression is required. Clinical signs that herald impending respiratory depression include somnolence, small pupils, and small tidal volumes.[58, 125] We also use oxyhemoglobin saturation monitoring, particularly in the first 24 hours of instituting this therapy.

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Pharmacokinetics and Pharmacodynamics of Inhalational Anesthetics in Infants and Children

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Inhalational anesthetics have long been the cornerstone of pediatric anesthesia. Their safe use in infants and children has been predicated on a thorough understanding of the physicochemical properties and physiologic effects of these drugs. In spite of a large body of experience, some clinicians still question whether neonates and young infants can tolerate inhalational anesthetics. In the last few years, this and other questions have been subject to a large volume of research. In this article, I review this research and discuss its application to the pharmacokinetics and pharmacodynamics of inhalational anesthetics in infants and children.

PHYSICOCHEMICAL PROPERTIES

The chemical structures of the potent inhalational anesthetics used in modern pediatric anesthesia belong to one of two categories: alkanes or ethers. The only alkane available for clinical use is halothane. Two ether anesthetics, isoflurane and enflurane, are currently in clinical use, and two more, desflurane and sevoflurane, are under investigation (Table 1). Isoflurane and enflurane are stereoisomers that differ only in the position of a single fluoride ion. Desflurane (formerly I-653), a methyl ethyl ether, differs in chemical structure from isoflurane by the substitution of fluoride for chloride on the alpha carbon of isoflurane, whereas sevoflurane, a methyl isopropyl ether, differs from isoflurane by the substitution of a trifluoromethyl group for chloride. Although the overall structure of all of these anesthetics is similar, the small differences in chemical structure confer differences in their solubilities and potencies (minimum alveolar concentration [MAC]) and in the case of desflurane, its boiling point (see Table 1). These differences in the physicochemical properties dramatically affect both the pharmacokinetics and pharmacodynamics of the potent inhalational anesthetics, in particular as they apply to pediatric anesthesia.

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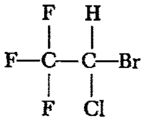
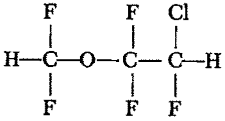
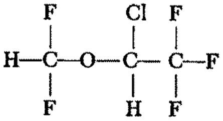
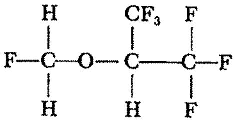
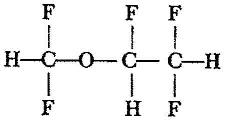
Table 1. *Physicochemical Properties of Inhalational Anesthetics*

	HALOTHANE	ENFLURANE	ISOFLURANE	SEVOFLURANE	DESFLURANE
Pharmacology					
Chemical structure	 $\mathrm{F{-}\overset{F}{\underset{F}{C}}{-}\overset{H}{\underset{Cl}{C}}{-}Br}$	 $\mathrm{H{-}\overset{F}{\underset{F}{C}}{-}O{-}\overset{F}{\underset{F}{C}}{-}\overset{Cl}{\underset{F}{C}}{-}H}$	 $\mathrm{H{-}\overset{F}{\underset{F}{C}}{-}O{-}\overset{Cl}{\underset{H}{C}}{-}\overset{F}{\underset{F}{C}}{-}F}$	 $\mathrm{F{-}\overset{H}{\underset{H}{C}}{-}O{-}\overset{CF_3}{\underset{H}{C}}{-}\overset{F}{\underset{F}{C}}{-}F}$	 $\mathrm{H{-}\overset{F}{\underset{F}{C}}{-}O{-}\overset{F}{\underset{H}{C}}{-}\overset{F}{\underset{F}{C}}{-}H}$
Molecular weight	197.4	184.5	184.5	200.1	168
Boiling point (°C)	50.2	56.5	48.5	58.6	23.5
Vapor pressure (mm Hg)	244	172	240	185	664
Odor	Mild, pleasant	Etheral	Etheral	Pleasant	Etheral
Solubility					
$\lambda_{b/g}$ adults	2.4	1.2	1.4	0.66	0.42
$\lambda_{b/g}$ neonates	2.14	1.78	1.19	0.66	—
$\lambda_{fat/g}$ adults	51.1	—	45	48	27
MAC					
MAC_{adults}	0.75	1.7	1.2	2.05	7.0
$MAC_{neonates}$	0.87	—	1.60	N/A	9.2

PHARMACOKINETICS

The speed at which the anesthetic partial pressure in the alveolus approaches the inspired anesthetic partial pressure depends on the rate of delivery of anesthetic to and removal (or uptake) from the lung. The wash-in of inhalational anesthetics depends on six factors (Table 2).[7] The first three factors determine the rate of delivery of the inhalational anesthetic to the alveolus; the second three determine the rate of removal from the alveolus. The rate of the increase of alveolar-to-inspired anesthetic partial pressures depends on the relative rates of delivery of anesthetic to and uptake from the alveolus.

Previous studies in adults used a five-compartment model to describe the rate of rise of alveolar-to-inspired anesthetic partial pressures.[3] The compartments were defined as the lungs, vessel-rich group, muscle group, a vague intertissue group, and fat group. Although pharmacokinetic studies in infants and children are lacking, a similar model would likely fit this age group as well. The following discussion focuses on the effects of age as they relate to the factors responsible for uptake and distribution of inhalational anesthetics (Table 2) in the first three compartments of the adult model of uptake and distribution: lungs, vessel-rich group, and muscle group.

The partial pressures of inhaled anesthetic in vital organs such as the brain and heart cannot be determined in vivo, although estimates of these pressures may be obtained indirectly, by measuring the end-tidal or alveolar anesthetic partial pressure. The partial pressure of the more soluble inhaled anesthetics in the vessel-rich group (brain, heart, kidney, splanchnic organs, and endocrine glands) lags behind that in the alveoli. However, the end-tidal partial pressure of the relatively insoluble inhalational anesthetics closely approximates the anesthetic partial pressure in the vessel-rich group during the first 15 to 20 minutes of anesthesia. Thus, the rate of rise of alveolar-to-inspired anesthetic partial pressures of relatively insoluble anesthetics approximates the rate of rise of anesthetic partial pressure in the vessel-rich organs during the early period of anesthesia.

The inspired concentration clinically affects only those anesthetics that are administered in high concentrations, i.e., nitrous oxide. The greater the inspired partial pressure of nitrous oxide, the more rapid the increase of alveolar-to-inspired anesthetic partial pressures. This phenomenon, termed the concentration effect, depends on both a concentrating effect and an increase in ventilation that results from an increased uptake of anesthetic.[7] While the rate of rise of alveolar-to-inspired partial pressures of nitrous oxide is very rapid in adults achieving an F_A/F_I of 0.8 within 10 minutes, it is even more rapid in neonates and infants, reaching a ratio of 0.9 within 5 minutes.[40, 45] Thus, the rate of rise of alveolar-to-inspired partial pressures of relatively insoluble anesthetics such as nitrous oxide is more rapid in neonates and infants than it is in adults.

Salanitre and Rackow[40] first demonstrated that the rate of rise of alveolar-to-inspired partial pressures of halothane is more rapid in infants and children than in adults. Subsequent studies reported similar observations with isoflurane and en-

Table 2. *Factors Responsible for the Wash-in of Inhalational Anesthetics*

1. Inspired concentration
2. Alveolar ventilation
3. Functional residual capacity
4. Cardiac output
5. Solubility
6. Alveolar-to-venous partial pressure gradient

flurane.[11] The more rapid rate of rise of anesthetic partial pressures in neonates compared with adults has been attributed to four differences between these two age groups (Table 3). The order of these four differences may reflect their relative contributions to the more rapid rate of rise of alveolar-to-inspired anesthetic partial pressure in neonates compared with adults.

The ratio of alveolar ventilation to functional residual capacity is a measure of the rate of wash-in of anesthetic into the alveoli. This ratio is approximately 5:1 in neonates compared with only 1.5:1 in adults. The greater ratio in neonates may be attributed to the threefold greater metabolic rate and therefore threefold greater alveolar ventilation in neonates compared with adults. Although alveolar ventilation changes with age, functional residual capacity (on a weight basis) remains fairly constant as age increases from neonates to young adults.

In adults, increases in cardiac output slow the rate of rise of alveolar-to-inspired anesthetic partial pressures.[7] Paradoxically, the higher cardiac index in neonates actually speeds the rise of alveolar-to-inspired anesthetic partial pressures. This has been attributed to the preferential distribution of the cardiac output to the vessel-rich group in neonates. The vessel-rich group receives a greater proportion of the cardiac output because it makes up 18% of the body weight in neonates compared with only 8% in adults. As a result of the increased blood flow, the partial pressure of anesthetics in the vessel-rich group equilibrates with that in the alveoli more rapidly in neonates than in adults. Since the uptake of anesthetic by tissues other than those of the vessel-rich group in neonates is small, the rapid equilibration of anesthetic partial pressures in the vessel-rich group and blood suggests that the partial pressure of anesthetic in venous blood returning to the lung rapidly approaches the partial pressure in the alveoli. Uptake of anesthetic from the lung then effectively ceases. Thus, the net effect of the greater cardiac output in neonates is to speed equilibration of anesthetic partial pressure in the vessel-rich group.

Inhalational anesthetics partition into two compartments in body fluids and tissues: (1) an aqueous phase that represents the smaller dissolved fraction and (2) a protein/lipid phase that binds the larger fraction of anesthetic. This is analagous to the distribution of oxygen in blood between the aqueous phase and the fraction bound to hemoglobin. Since anesthetics move along partial pressure and not concentration gradients within the nongas-filled organs of the body, the rate of rise of alveolar anesthetic partial pressure and therefore the anesthetic partial pressure in blood determines how rapidly anesthetics move into tissues.

The solubility of an inhalational anesthetic is the ratio of the anesthetic concentrations in two phases when the anesthetic partial pressures in the two phases are equal. As the solubility of an anesthetic in blood or tissues decreases, the amount of anesthetic taken up by that phase decreases proportionately and therefore the time required to achieve partial pressure equilibrium also decreases. Thus, the rate of rise of alveolar-to-inspired partial pressures of inhalational anesthetics varies inversely with the solubility in blood as follows: nitrous oxide > desflurane > sevoflurane > isoflurane > enflurane > halothane > methoxyflurane.[7, 53]

The solubility of a potent inhalational anesthetic also determines the speed of the alveolar partial pressure response to changes in the inspired concentration. For

Table 3. *Factors Responsible for the Rapid Wash-in of Inhalational Anesthetics in Infants*

1. Greater alveolar ventilation to functional residual capacity ratio[40]
2. Greater fraction of the cardiac output distributed to the vessel-rich group
3. Lower tissue/blood solubility[27]
4. Lower blood/gas solubility[28]

example, the rate of increase of alveolar-to-inspired anesthetic partial pressures is more rapid with inhalational anesthetics with low blood solubilities (i.e., desflurane and sevoflurane) compared with those with greater solubilities (see Table 1).[53] After a stepwise change in the inspired concentration of these anesthetics with low blood solubility, we can expect the end-tidal concentration to equilibrate rapidly with the new inspired concentration. Therefore, the lower solubilities of these newer potent inhalational anesthetics allow anesthetists to control the depth of anesthesia more rapidly and effectively than with the more soluble inhalational anesthetics.

How does age affect the blood solubility of inhalational anesthetics? The blood solubilities of the inhalational anesthetics halothane, isoflurane, enflurane, and methoxyflurane are 18% less in neonates than they are in adults.[28] The lower solubility in neonates correlates with lower albumen and globulin concentrations for the less soluble anesthetics isoflurane and enflurane, and with albumen and triglycerides for the more soluble anesthetics, halothane and methoxyflurane. In contrast, we noted that age has no significant effect on the solubility of the less soluble anesthetic sevoflurane.[30] In addition, age-related differences in hemoglobin, α_1-acid glycoprotein, and prematurity do not contribute significantly to the differences in anesthetic solubility in blood.[25, 30, 44] Thus, lower blood solubilities contribute to the more rapid equilibrium of alveolar and blood anesthetic partial pressures in neonates compared with adults.

The solubilities of the inhalational anesthetics, halothane, isoflurane, enflurane, and methoxyflurane, in the vessel-rich group in neonates are approximately one half those in adults (Fig. 1).[27] These lower tissue solubilities may be attributed to two differences in the composition of tissues in neonates compared with those in adults: (1) greater water content and (2) decreased protein and lipid concentrations. Thus, the lower solubility of inhalational anesthetics in tissues, like blood, speeds the rate of rise of alveolar-to-inspired anesthetic partial pressures in neonates compared with adults.

The time constant (τ) for equilibration of anesthetic partial pressure in the brain is described by the following ratio:

$$\tau = \frac{\text{Volume of the brain (mL)} \times \text{brain/blood solubility}}{\text{Brain blood flow (mL/min)}}$$

where the time constant is the time for the partial pressure of anesthetic in the brain to reach 66% of the partial pressure in the blood. If the brain blood flow is approximately 50 mL/min/100 g of brain and the brain/blood solubility for a particular inhalational anesthetic is 2.0, then the time constant is calculated as follows:

$$\tau = \frac{100 \text{ mL} \times 2}{50 \text{ mL/min}} = 4 \text{ min}$$

assuming the density of the brain tissue is 1 g/mL. Thus, the time to 95% equilibration of anesthetic partial pressures (i.e., four time constants) is 16 minutes. If the brain/blood solubility were halved to 1.0 as it might be in the neonate, then the time to 95% equilibration would be reduced to only 8 minutes. Hence, the time to equilibration of anesthetic partial pressure within the brain of the neonate would be approximately one half that of the adult. Since the speed of onset of anesthetic effects on the brain is more rapid in the neonate than in the adult, high inspired concentrations (the overpressure technique) may produce exaggerated pharmacodynamic responses earlier in the induction sequence in neonates compared with that in adults. This typifies how a basic understanding of uptake and distribution can provide the much needed insight into the effects of inhalational anesthetics in neonates and small infants.

While the pharmacokinetics of inhalational anesthetics during the first 15 to 20

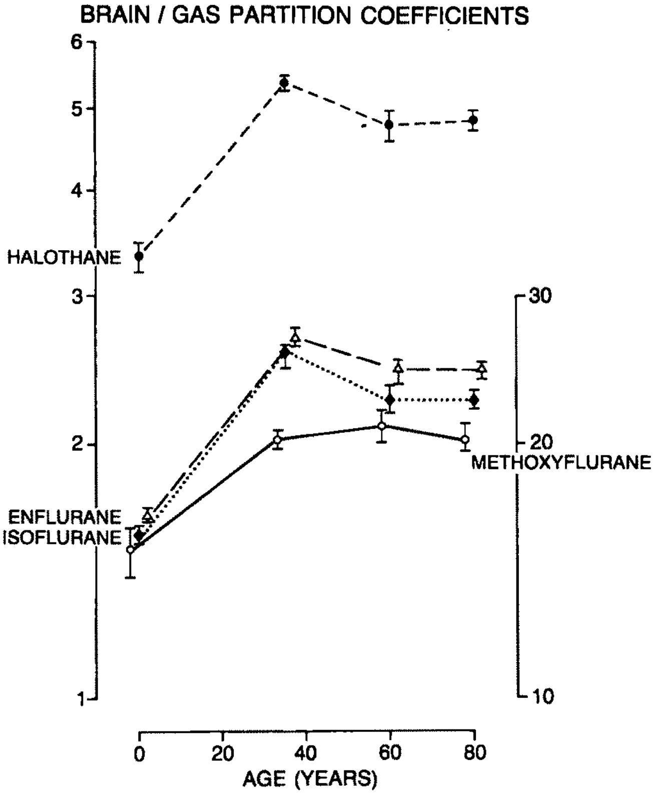


Figure 1. Effect of age on the solubility of isoflurane, enflurane, halothane, and methoxyflurane in the human brain. The solubility of all anesthetics in the neonatal brain is less than that in older adults. (*From* Lerman J, Schmitt BI, Willis MM, et al: Effect of age on the solubility of volatile anesthetics in human tissues. Anesthesiology 65:63–67, 1986; with permission.)

minutes depends primarily on the characteristics of the vessel-rich group, the pharmacokinetics in the subsequent 20 to 200 minutes depend on the uptake of anesthetic by the muscle group.[7] The solubility of inhalational anesthetics in skeletal muscle varies directly with age in a logarithmic manner.[27] Thus, the lower solubility of inhalational anesthetics in muscle in neonates speeds the rise of alveolar to inspired anesthetic partial pressures during this period compared with adults. This effect of age on the solubility of anesthetics in muscle has been attributed to age-dependent increases in protein concentration in the first five decades of life and in fat content in the subsequent three decades of life.

The net effect of all of these differences between neonates and adults is to speed the equilibration of anesthetic partial pressures in alveoli and tissues and thereby speed the rate of rise of alveolar-to-inspired anesthetic partial pressures in neonates. However, these differences may not affect all inhalational anesthetics to similar extents, i.e., the difference in the rate of rise of alveolar-to-inspired partial pressures of desflurane and sevoflurane in neonates when compared with adults may be less than for the more soluble anesthetics. This hypothesis awaits verification in humans.

The physiologic factors that determine the rate of rise of alveolar-to-inspired anesthetic partial pressures affect soluble and insoluble anesthetics differently. Alveolar ventilation and cardiac output exert greater effects on more soluble anesthetics (i.e., methoxyflurane) than on the less soluble anesthetics (i.e., desflurane and sevoflurane).[7] The effects of shunts on the rate of rise of alveolar-to-inspired anesthetic partial pressures are less clear. In general, left-to-right shunts with only small changes in cardiac output do not significantly affect the pharmacokinetics of potent inhalational anesthetics. In contrast, right-to-left shunts exert a significant effect on the wash-in of anesthetics. Furthermore, the magnitude of the effect of the right-to-left shunt depends on the solubility of the anesthetic: these shunts affect the relatively insoluble anesthetics to a greater extent than the more soluble anesthetics.[7] The anatomic level of right-to-left shunts may be either intrapulmonary (as in the case of an endobronchial intubation) or intracardiac. The role of shunts in pediatric anesthesia has only recently become a serious concern, ever since the introduction of desflurane and sevoflurane. To understand the effect of the shunt on the pharmacokinetics of inhalational anesthetics, one might consider a simplified lung in which each lung is represented by one alveolus and each lung is perfused by one pulmonary artery. When the tracheal tube is positioned in the midtrachea, ventilation is divided equally between both lungs, thereby yielding equal anesthetic partial pressures in the two pulmonary arteries. However, if the tube is then positioned in a bronchus, all of the ventilation is delivered to one lung, i.e., the ventilation to that lung is doubled whereas ventilation to the second lung is zero. Under these conditions, the partial pressure of CO_2 remains unchanged. When a soluble anesthetic is administered, the partial pressure of anesthetic in the combined pulmonary arteries is approximately the same as that when the tube was in the trachea since ventilation compensates for the almost 50% shunt through the nonventilated lung.[7] However, the effect of a right-to-left shunt is very different with a relatively insoluble anesthetic. For such an anesthetic, changes in ventilation exert only a small effect on the wash-in of the anesthetic.[7] Thus, even though ventilation to the lung doubles with an endobronchial intubation, F_A/F_I increases less than 10% as a result of the increased ventilation and is unable to compensate for the 50% shunt. Induction of anesthesia with a relatively insoluble anesthetic is thereby slowed in the presence of a right-to-left shunt. Furthermore, in the presence of these shunts, end-tidal concentrations may significantly underestimate the anesthetic partial pressure in the blood. As desflurane and sevoflurane are introduced into clinical practice, it is important to consider these factors and their relative roles in affecting induction of anesthesia.

The metabolism of inhalational anesthetics is discussed in the following sections on renal and hepatic effects.

The wash-out of anesthetics follows an exponential decay curve (the inverse of the wash-in curve). The speed of wash-out varies directly with the blood/gas solubility of the anesthetic in adults.[53] Recovery of motor function in rats parallels the wash-out of inhalational anesthetics:[8] desflurane > sevoflurane > isoflurane > halothane. Although similar studies in infants and children are not available, it seems reasonable to expect that the order of wash-out of inhalational anesthetics in children will be similar to that in adults.

PHARMACODYNAMICS

Minimum Alveolar Concentration

The MAC of inhalational anesthetics is the alveolar anesthetic concentration at which 50% of patients do not move in response to skin incision. In the pediatric age range, the effect of age on MAC is extremely important.

Previous investigators reported an inverse relationship between MAC and age: they observed that MAC is greatest in infants 0 to 6 months of age and steadily decreases as age increases from infants to adolescents.[14] However, they considered neonates and infants 1 to 6 months of age as a uniform age group with the same MAC value and anesthetic requirements. In fact, acute circulatory depression occurred in 70% of the neonates when they were anesthetized with only 1 MAC halothane and 60% nitrous oxide. In an attempt to explain the profound circulatory depression in neonates anesthetized with inhalational anesthetics, we sought to determine the anesthetic requirements of halothane in neonates as a group distinct from older infants 1 to 6 months of age.[26] We found that the MAC of halothane was 25% less in neonates (0.87 ± 0.03%) than it was in older infants 1 to 6 months of age (1.20 ± 0.06%). Cameron et al[2] found a similar relationship between age and the MAC of isoflurane in infants and children (Fig. 2). MAC of isoflurane in neonates was 17% less than it was in older infants 1 to 6 months of age. Recent measurements of the MAC of desflurane in infants and children demonstrated similar age-related changes in MAC, i.e., MAC increased as age decreased, reaching a zenith during infancy.[47] MAC for desflurane was approximately 9.4% for neonates and infants 1 to 12 months of age and 8.5% for children 1 to 12 years of age. Interestingly, the difference between the peak MAC of desflurane in infants and that of neonates was only 7%. The ratio of the peak MAC in infancy to that in neonates correlated with the lipid solubility of volatile anesthetics. The markedly lower potency (i.e., higher MAC) of desflurane limits the inspired concentrations of other gases such as nitrous oxide and oxygen. The MAC of sevoflurane in adults is 1.71% to 2.05%[18, 42] and in newborn swine is 2.12%.[24] The MAC of sevoflurane in infants and children is currently under investigation. These data suggest that MAC for all potent inhalational anesthetics increases as age decreases, reaching a zenith in infancy and decreases thereafter as age decreases.

The anesthetic requirements of inhalational anesthetics in preterm neonates have also been investigated.[22] The MAC (mean ± SD) of isoflurane in preterm neonates less than 32 weeks (1.28 ± 0.17%) is 10% less than it is in neonates of 32 to 37 weeks gestational age (1.41 ± 0.18%), which in turn is 12% less than it is in full-term neonates (1.60 ± 0.03%) (Fig. 2). These data demonstrate that MAC not only decreases with decreasing gestational age from full-term to preterm infants of 24 weeks gestational age, but that the MAC of isoflurane in these very young preterm infants is not zero.

The cause of these age-dependent changes in MAC remains unclear. Several possible factors including maturational changes in the CNS and neurohumoral factors have been proffered as possible explanations for this observation, but at this time the cause remains obscure.

The Central Nervous System

All inhaled general anesthetic agents depress the activity of the CNS. This occurs in association with a decrease in cerebral metabolic rate. However, all of the potent inhaled anesthetic agents dilate the cerebral vasculature, with an accompanying increase in intracranial volume and if critical, an increase in intracranial pressure. In adults, the cerebral vasculature remains responsive to carbon dioxide even under general anesthesia. Thus, increases in intracranial pressure may be attenuated if the lungs are hyperventilated during anesthesia. The effects of inhalational anesthetics on the CNS in children have not been elucidated. Preliminary evidence suggests that cerebral blood flow velocity in children varies directly with the end-tidal carbon dioxide partial pressure during halothane anesthesia.[23] Cerebral blood flow velocity increases as the concentration of halothane increases,[21] whereas it does not change significantly in the presence of increasing concentrations of isoflurane. Further studies are required to validate these preliminary findings.

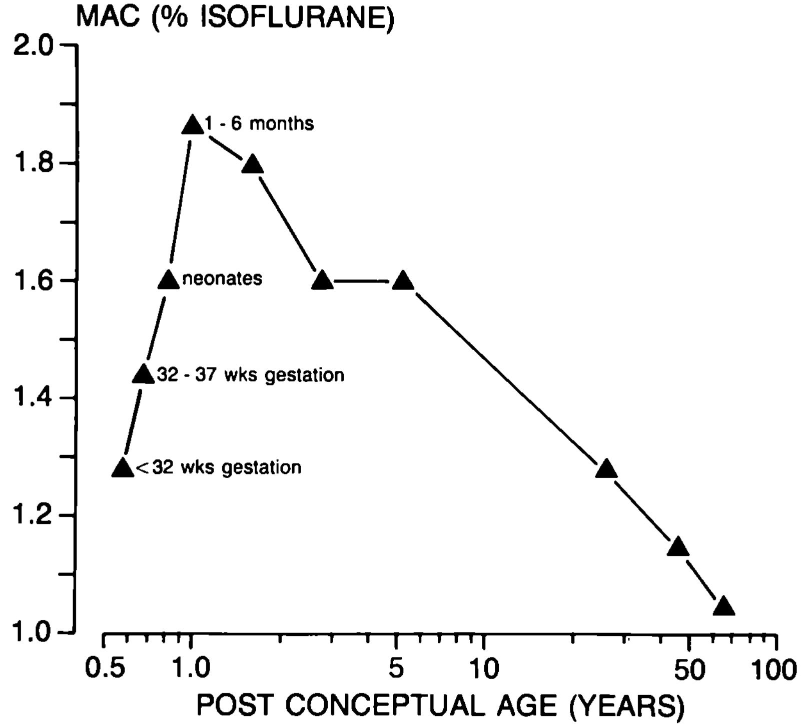


Figure 2. Effect of age on the MAC of isoflurane. MAC increases as age decreases, reaching a zenith in infants 1 to 6 months of age and decreasing thereafter as age decreases through the 40 weeks of gestation. Postconceptual age is the sum of gestational and postnatal ages. (*From* LeDez KM, Lerman J: The minimum alveolar concentration (MAC) of isoflurane in preterm neonates. Anesthesiology 67:301–307, 1987; with permission.)

Enflurane, unlike other commonly used inhalational anesthetics, may precipitate seizure activity on the electroencephalogram, and in some patients convulsive movements have been observed. This is particularly likely to occur with high concentrations of enflurane and in the presence of hypocapnea. It is advisable to avoid enflurane in children with a history of epilepsy.

The CNS effects of desflurane and sevoflurane in humans have not been fully elucidated. We know that neither desflurane nor sevoflurane initiate epileptogenic cortical activity.[39, 43] In addition, both anesthetics decrease cerebral blood flow in proportion to their effects on the cerebral metabolic rate for oxygen consumption similar to isoflurane.[39, 43]

Circulation

In infants and children, halothane decreases systolic arterial pressure in a dose-dependent manner, decreases heart rate, depresses myocardial contractility, and minimally vasodilates the peripheral vasculature.[35, 51] Although isoflurane decreases systolic arterial pressure to a similar extent as halothane, it increases heart rate, depresses myocardial contractility to a lesser extent than halothane or not at all and vasodilates the peripheral vasculature to a greater extent than halothane.[35, 51] The baroreflex response is depressed in a dose-dependent manner with both halothane and isoflurane, albeit to a lesser extent with isoflurane. Cardiac output is decreased to a greater extent during halothane anesthesia than it is during isoflurane anesthesia, although atropine has been shown to reverse this effect in the presence of halothane.[1]

It had been suggested that the incidence of hypotension in neonates is more than twice that in infants 1 to 6 months of age at *equal* concentrations of inhalational anesthetics. This occurred at a time when the MAC values of halothane in neonates and infants 1 to 6 months of age were believed to be equal.[14] However, when the same circulatory responses were compared at *equipotent* (i.e., at ≈1 MAC) concentrations of halothane,[26] heart rate, and systolic arterial pressure decreased to similar extents in both neonates and older infants 1 to 6 months of age. Although the circulatory responses to MAC-equivalent concentrations of isoflurane in neonates and infants have not been forthcoming, circulatory responses in newborn swine would suggest that halothane and isoflurane depress the newborn heart similarly.[24] The circulatory responses to desflurane in neonates are also similar to those of older infants at equipotent concentrations.[47] Whereas heart rate was maintained or decreased slightly at ≈1 MAC desflurane in neonates and infants compared with awake values, systolic arterial pressure decreased significantly (approximately 30%) in all infants and older children. These studies provided the much needed data to dispel the previous notion that neonates were more susceptible to circulatory depression by inhalational anesthetics than were older infants.

Although neonates are no more susceptible to circulatory depression than older infants at equipotent concentrations, the determinants of the circulatory depression in neonates has been subject of several studies. Data from rabbits suggest that halothane-induced circulatory depression in the neonate may be attributed in part, to effects of halothane on contractile protein, cell membranes, and intracellular dynamics of calcium ions. The negative inotropic effect of inhalational anesthetics is largely reversible by calcium. The circulatory depression may also be attributed to an immature sympathetic nervous system, vagal predominance, and reduced vascular tone. Furthermore, halothane and isoflurane depress the baroreflex response in the neonate.[13, 34] Studies in a newborn swine model demonstrated that halothane depressed the circulation to a similar extent as isoflurane, while sevoflurane depressed the circulation to a lesser extent than either halothane or isoflurane at equipotent anesthetic concentrations.[24]

The effects of inhalational anesthetics on cardiac rhythm vary among the anesthetics. Halothane may cause bradycardia, which has been attributed to a direct effect on the sinoatrial node as well as to an effect mediated through the vagus nerve. The latter effect is readily reversed by atropine.[1] Bradycardia is particularly marked in newborns, presumably because vagal influences predominate over the sparse sympathetic innervation of the myocardium in this age group. Junctional rhythms are common under general anesthesia, especially when halothane is used. Atrial or ventricular ectopic beats are rare unless hypercapnea or hypocapnea has occurred. Halothane sensitizes the myocardium to catecholamines, and life-threatening rhythm disturbances may occur if epinephrine is used in patients during halothane anesthesia. In contrast, isoflurane, desflurane, and sevoflurane do not sensitize the myocardium to catecholamines to the same extent.[16, 17, 50]

The circulatory responses to isoflurane in the preterm infant have been the subject of several investigations.[10, 22] In preterm neonates of less than 32 weeks gestational age who are anesthetized with ≈1 MAC isoflurane, we found that heart rate and systolic arterial pressure decreased to similar extents as in older preterm neonates 32 to 37 weeks.[22] Furthermore, these circulatory responses were similar to those observed with halothane in full-term neonates. The baroresponse is immature in the preterm neonate and is relatively ineffective in the presence of halothane.[13]

Most preterm neonates who present for surgery have one of two major conditions: bowel obstruction/pathology or patent ductus arteriosus. These neonates are intravascular volume depleted because of third-space fluid losses or overzealous diuresis. In our study of the MAC of isoflurane in preterm infants, lactated Ringer's solution or albumen (10–15 mL/kg) was administered to maintain the systolic arterial pressure at greater than or equal to 40 mm Hg as the concentration of isoflurane was increased slowly in increments of 0.5% isoflurane. With these precautions, the decrease in systolic arterial pressure at ≈1 MAC isoflurane was similar to that reported previously with fentanyl.[10, 22] Atropine was not administered during induction of anesthesia in the MAC study in order to quantitate the hemodynamic responses to isoflurane. However, in clinical practice, IV atropine is a prudent adjunct since it maintains a rapid heart rate and thus cardiac output in infants and children.[1] Thus, the three important considerations for maintenance of circulatory homeostasis during administration of potent inhalational anesthetics to preterm neonate are (1) atropine, 0.02 mg/kg IV at induction; (2) slow incremental increases in the concentration of potent inhalational anesthetics; and (3) lactated Ringer's solution or albumen (≥10 mL/kg) as needed.

Respiratory Responses

Anesthesia is frequently induced by inhalation. Halothane is commonly used for this purpose. The popularity of halothane may be attributed to its nonirritating odor, moderate solubility in blood and tissues, high potency (i.e., low MAC), and moderate degree of respiratory depression. However, halothane depresses ventilation in a dose-dependent manner by decreasing tidal volume and attenuating the response to carbon dioxide. This respiratory depression is also attenuated, in part, by an increase in the respiratory rate.[29, 33, 52] Intercostal muscle activity is attenuated and paradoxical breathing may occur at concentrations greater than or equal to 1% end-tidal halothane. This latter effect is most pronounced in the preterm and full-term neonate and infant.

In the neonate with a very compliant chest wall, inhibition of intercostal activity may lead to paradoxical chest wall movement and hence to less effective ventilation. This effect is particularly marked in any degree of resistance or obstruction to ventilation. If the resistance of the upper airway or respiratory circuit is sufficiently great, apnea may occur. Failure of the chest wall to maintain its normal role during ventilation also contributes to a decrease in the functional residual capacity. This decrease in functional residual capacity may persist into the postoperative period and contribute to an overall poor pulmonary performance and large alveolar-to-arterial oxygen difference.

The ventilatory response to hypoxemia in adults is also severely depressed by inhaled anesthetics. The mechanism of this response is likely depression of the peripheral chemoreceptor. The effects of inhalational anesthetics on the ventilatory response to hypoxemia in children remain undetermined.

Although tidal volume decreases progressively as the depth of anesthesia increases, this effect is attenuated by an increase in the respiratory rate with most inhalational anesthetics. Enflurane depresses respiration to a greater extent than both halothane and isoflurane[33, 52] since the respiratory rate remains near awake values despite a dose-dependent decrease in tidal volume. In adults, desflurane depresses respiration to a similar extent as isoflurane. Sevoflurane depresses respiration to a similar extent as halothane until 1.4 MAC, after which respiratory depression with sevoflurane exceeds that of halothane.[5] Although these effects may be important during induction and maintenance of anesthesia with sevoflurane, it is equally important to recognize that the low blood solubility of sevoflurane and resultant rapid wash-out of anesthetic will minimize the duration of respiratory depression postoperatively.[6]

Both tidal volume and respiratory rate are, however, extremely variable during spontaneous ventilation in anesthetized patients. Such variation may be attributed to varying levels of surgical stimulation. The increased respiratory rate seen with many inhaled anesthetic agents such as halothane was originally thought to be due to sensitization of stretch receptors in the lung, but is now recognized as a central effect. The pattern of spontaneous ventilation (low tidal volume and rapid respiratory rate) during anesthesia and the susceptibility to apnea in the presence of a resistive load, dictates that the optimal anesthetic circuit for infants and children should contain minimal apparatus dead space and resistance.

Although halothane is most commonly used for induction of anesthesia in children, anesthesia may also be induced with the ether anesthetics isoflurane, enflurane, desflurane, and sevoflurane. Favorable physicochemical properties[27, 28] (see Table 1) might lead us to anticipate that these anesthetics are more effective induction agents than halothane. However, the irritant effects of isoflurane and enflurane on the upper airway and their depressant effects on the respiratory system more than offset the favorable physicochemical properties. The irritant effects of isoflurane on the upper airway are manifested by a higher incidence of breath holding, coughing, salivation, excitement, laryngospasm, and arterial oxygen desaturation during induction of anesthesia than with halothane.[9, 31, 36, 37]

The induction characteristics of desflurane in unpremedicated infants and children up to 12 years of age have recently been reported.[48] Although the eyelash reflex was lost quickly after commencement of desflurane in oxygen, a stormy induction ensued in many of these patients. Inductions were punctuated by periods of breath holding (50% of patients), mild laryngospasm (30% of patients), and coughing (36% of patients), much the same as reported previously with isoflurane.[9, 31, 36, 37] Although all patients were preoxygenated and anesthetized with desflurane in 100% oxygen, arterial oxygen saturation fell below 90% during induction of anesthesia in 18% of the patients. Severe laryngospasm that required succinylcholine occurred in 3% of the patients. Based on these data, the advantages of the physicochemical properties of desflurane for rapid induction of anesthesia in infants and children are overshadowed by its irritant effects on the upper airway. These difficulties will limit the role of desflurane as an induction agent in infants and children. In contrast, two studies from Japan reported favorable induction characteristics with sevoflurane in healthy children.[32, 41] There were few complications during induction of anesthesia and no evidence of airway irritation. Although pediatric trials with sevoflurane in North America are currently in progress, these published data from Japan together with preliminary evidence from our institution suggest that sevoflurane may be an effective induction agent in children.

Many techniques are available to smooth induction of anesthesia with inhalational anesthetics, particularly those that irritate the upper airway. Nitrous oxide pretreatment for 60 to 90 seconds, premedicants,[38] anticholinergics,[4] and scented masks or liquids have all been used to attenuate airway reflex responses with variable success. For the purposes of an inhalational induction, I increase the concentration of halothane in increments of 0.5% every two to three breaths until 3 or 4 MAC is achieved. With sevoflurane, the concentration may be increased in increments of 1.5% every two to three breaths. The inspired concentration is then titrated to clinical responses. Induction of anesthesia with a single breath of 5% halothane in children has also been successful. A similar approach has been taken with isoflurane although the induction must be accompanied with continuous positive airways pressure and assisted ventilation to rapidly deepen anesthesia and reduce the incidence of airway reflex response.

Four of the factors that determine the speed of induction of anesthesia by mask in children are (1) solubility, (2) odor, (3) rate of increase of the inspired concentration, and (4) maximum inspired concentration.

Solubility and odor are two physicochemical properties of inhalational anesthetics. It is well known that the speed of induction of anesthesia varies inversely with the solubility of inhaled anesthetics. However, as the solubility decreases, MAC increases (i.e., potency decreases). Thus, higher concentrations of the anesthetic are required to induce anesthesia. This may be achieved most effectively in children with anesthetics that have pleasant odors. Although artificial fragrances may be used to facilitate facemask acceptance in children, there are few techniques available to mask the odor of pungent anesthetics and prevent airway irritation. Inhalational inductions with the latter anesthetics are difficult and protracted because of a high incidence of airway reflex response.

The rate of increase of the inspired concentration and the maximum inspired concentration both affect the speed of induction of anesthesia. The rate of increase in the inspired concentration is usually limited by airway reflex responses to the odor of the inhalational anesthetic. Overpressure is a technique used to speed induction of anesthesia by increasing the inspired concentration to several multiples of MAC in order to speed delivery of anesthetic to the vessel-rich group. As induction continues, the inspired concentration is decreased to clinically acceptable concentrations. However, if the maximum inspired concentration is limited by the maximum concentration of the vaporizer, overpressure may not be as effective and anesthesia may not be induced as rapidly as predicted based on physicochemical properties. In the case of halothane, the maximum inspired concentration available on the vaporizer is 5%. This corresponds to approximately five times MAC in young children. In contrast, sevoflurane is delivered by vaporizers with a maximum concentration of 5% in Japan. Because of its higher MAC, this maximum inspired concentration of sevoflurane corresponds to only 2.5 MAC. This restriction on the maximum concentration limits the effectiveness of the overpressure technique with sevoflurane and could delay induction of anesthesia. For example, after 10 minutes of an inhalational induction in adults, F_A/F_I for halothane is 0.6 and for sevoflurane is 0.8.[53] Thus, for an inspired concentration of 5%, the corresponding alveolar fraction is 3.0% for halothane and 4.0% for sevoflurane. Given the relative MAC values for adults, these alveolar concentrations correspond to 4 MAC halothane, but only 2 MAC sevoflurane. Despite the favorable physicochemical properties of sevoflurane, induction of anesthesia may not be as rapid as it could be because of the limitations imposed by the current vaporizer design. The maximum inspired concentration of sevoflurane available with modern vaporizers must be increased to 8% to 10% to facilitate rapid induction of anesthesia with sevoflurane.

Two feedback mechanisms modulate the depth of anesthesia during ventilation with inhalational anesthetics: respiratory and cardiovascular. During spontaneous ventilation, respiratory depression limits the depth of anesthesia. As the depth of anesthesia increases, alveolar ventilation decreases, the patient lightens from anesthesia, and spontaneous respiration increases. This is a negative feedback effect. This protective mechanism permits the use of inspired concentrations of inhalational anesthetics severalfold greater than MAC (overpressure technique) to induce anesthesia rapidly. Moreover, the negative feedback effect of respiratory depression protects against excessive circulatory effects of the high inspired concentrations. However, if ventilation is controlled, this protective mechanism is bypassed. The alveolar-to-inspired anesthetic partial pressure ratio increases relentlessly as the cardiac output steadily decreases. This is a positive feedback effect. This leads to a downward spiral that could lead to cardiovascular collapse and death if the cycle is not broken. Studies in dogs have shown that during spontaneous ventilation, concentrations of halothane up to 6% can be tolerated without cardiovascular collapse, whereas if ventilation is controlled, concentrations of halothane greater than or equal to 4% will cause profound cardiovascular depression and death.[12] High concentrations of inhalational anesthetics are commonly administered during inhalational inductions either as stepwise increases in concentration or as a single breath high concentration. These high concentrations can be tolerated providing spontaneous ventilation is maintained. However, if the pattern of ventilation changes from spontaneous to controlled, then circulatory collapse may occur, particularly in neonates and small infants who have limited cardiovascular reserve. Thus, the inspired concentration of inhalational anesthetics must be decreased when the pattern of ventilation changes from spontaneous to controlled in order to minimize the risk of circulatory collapse.

Renal Effects

Inhalational anesthetics depress renal function via four possible mechanisms: cardiovascular, sympathetic, neuroendocrine, and metabolic. While the first three mechanisms pose no direct threat to renal function in most patients, the metabolic effects, i.e., the liberation of inorganic fluoride, are a potential concern. In vivo metabolism of enflurane, sevoflurane, and methoxyflurane liberates inorganic fluoride ions. Very little inorganic fluoride is released after metabolism of isoflurane, halothane, and desflurane. Fluoride blocks distal tubular active resorption of sodium and/or chloride in the loops of Henle, thereby inducing a vasopressin-resistant high-output renal failure. Although it is generally accepted that nephrotoxicity can complicate general anesthesia when the serum concentration of inorganic fluoride exceeds the theoretical toxic threshhold concentration of 50 μmol/L, many now believe that the risk of nephrotoxicity depends more on the area under the concentration-time profile of inorganic fluoride than on the peak serum concentration.

The peak serum concentrations of inorganic fluoride after exposure to inhalational anesthetics follow this order: methoxyflurane > enflurane ≈ sevoflurane > isoflurane ≈ halothane ≈ desflurane. With the exception of methoxyflurane, however, the peak serum concentration of inorganic fluoride after administration of a potent inhalational anesthetic does not reach the nephrotoxic threshhold. In the case of methoxyflurane, nephrotoxicity was reported in adults, and this led to its disappearance from clinical use. In contrast to the adult experience, fluoride-induced nephrotoxicity has never been established in children, and methoxyflurane continues to be used at our institution. The failure of methoxyflurane to induce nephrotoxicity in children may be due to the lower peak serum concentrations of inorganic fluoride after an equivalent dose of methoxyflurane is administered in children and adults.[46] The lower concentrations of fluoride has been attributed to a decreased metabolism of methoxyflurane, greater uptake of fluoride by bone, increased excretion of fluoride ions, or a reduced renal sensitivity to fluoride in children.[46] Preliminary data suggest that sevoflurane will pose no greater a risk of fluoride-induced nephrotoxicity than enflurane, although the studies are incomplete. One important advantage of sevoflurane is that its low solubility in blood and tissues will minimize the duration of exposure to inorganic fluoride.

Hepatic Effects

Inhalational anesthetics are metabolized to varying degrees in vivo. The extent of metabolism in adults follows this order: methoxyflurane (50%) > halothane (15%–25%) > sevoflurane (4.6%) > enflurane (2.4%) > isoflurane (0.2%) > desflurane (0.02%). Metabolism of inhalational anesthetics is probably less in neonates and infants than it is in adults. This may be attributed to several factors including reduced activity of the hepatic microsomal enzymes, reduced fat stores, and more rapid elimination of inhaled anesthetics in infants and children. Halothane and, more recently, enflurane, have been suspected of causing liver dysfunction. Indeed several cases of postoperative liver failure have been attributed to "halothane hepatitis" in children.[19] The exact mechanism that leads to this response remains unclear, although some have speculated that it may be caused by a specific metabolite of halothane. This putative toxic substance may be produced when the reductive pathway for halothane biotransformation in the liver microsomes is active as, e.g., when hepatic blood flow is impaired and liver enzyme induction has occurred. Such induction might be caused by other drugs including barbiturates, phenytoin, and rifampin. Since the reductive metabolic pathways in the liver are poorly developed in infants and children, this may account for the very low incidence of halothane hepatitis in children, although recently this has been challenged.[49] While some have suggested that the routine use of multiple anesthetics with halothane in children should be reevaluated, the fact that millions of repeated halothane anesthetics have been administered to children without ill effects lends support to our position that there is insufficient evidence at present to avoid repeat halothane anesthetics in infants and children.

Stability

The increased use of soda lime absorbers has prompted investigations of the disposition of inhalational anesthetics in closed and semiclosed circuits. Isoflurane and desflurane are neither absorbed nor metabolized by soda lime. At high temperatures, halothane is degraded to 2-bromochloroethylene, although the concentration of this degradation product does not exceed 1/200th of the lethal concentration. Sevoflurane is absorbed to a small extent in a dynamic closed circuit and is also degraded in part, by alkaline hydrolysis in the presence of soda lime.[15] Of the five degradation products identified, compounds A and B appear in the greatest concentrations. Compound A, which may reach concentrations as high as 20 to 30 ppm in a low-flow closed circuit model, accumulates to only a small fraction of its toxic concentration. While initial studies with both static and in vitro models of sevoflurane administration through soda lime cannisters raised concerns about the safe use of this agent in the presence of soda lime, more recent evidence has not supported this concern. Further studies are required to fully clarify the risk, if any, associated with the use of sevoflurane in the presence of soda lime.

SUMMARY

Inhalational anesthetics remain the cornerstone of pediatric anesthesia. Recent insights into the pharmacokinetics and pharmacodynamics of inhalational anesthetics have provided clinicians with a greater understanding of the effects of these anesthetics in infants and children with a wide range of clinical conditions. We await the introduction of desflurane and sevoflurane, two new and exciting inhalational anesthetics that could help us deal more effectively with the increasing challenges that we face in pediatric anesthesia.

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Neuromuscular Blocking Drugs

*Barbara W. Brandom, MD**

There are two general categories of new developments in the study of neuromuscular blocking drugs in pediatric patients. One category consists of recent studies that carefully document the effects of commonly used neuromuscular blocking drugs. The second category consists of reports of the clinical development of new drugs in pediatric patients. Documentation of the effects of new neuromuscular blocking drugs has been more complete in pediatric patients, before marketing of the new drug, than has documentation of the effects of new sedatives or analgesics in this patient population. This is due, at least in part, to the relative ease with which the effects of neuromuscular blocking drugs can be documented. Although measurement of neuromuscular function can be difficult, it is more easily made objective than is the measurement of anxiety or pain, especially in preverbal patients. Therefore, the anesthetist who cares for pediatric patients occasionally can turn to readily available documentation and find reasonable age-adjusted recommendations for the use of recently developed neuromuscular blocking agents. The effects of drugs that have been available for a longer time have not been as carefully documented. Studies published in the last few years have usefully expanded on earlier dosage recommendations, made more detailed observations of onset and recovery from paralysis, and acknowledged some of the potential side effects of the neuromuscular blocking drugs that are commonly administered to pediatric patients. First, studies that add new information about drugs that have been used clinically for many years are discussed, and then drugs undergoing clinical development in 1990 and 1991 are described.

SUCCINYLCHOLINE

As is the case with several other neuromuscular blocking drugs, the dose-response relationship of succinylcholine has recently been subject to reevaluation. Previous studies documented that when succinylcholine was administered on the basis of milligram per kilogram of body weight during nitrous oxide–thiopental anesthesia, neonates and infants required more drug than did children, and both required more than did adults to produce the same effect.[41] The respective ED_{90}s, or doses estimated to produce 90% depression of evoked neuromuscular function, were 517 μg/kg in neonates, 608 μg/kg in infants, 352 μg/kg in children, and

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290 μg/kg in adults. Because of this and the variability in response to small doses of succinylcholine, the recommendation was made that 3 mg/kg of succinylcholine be administered to facilitate intubation for neonates and infants, while 2 mg/kg was considered more appropriate for children during balanced anesthesia.[41] Note that these doses are five to almost seven times the ED_{90}s. This study confirms earlier observations that age-related differences in response to succinylcholine are decreased, even abolished, by referencing the dose to body surface area rather than to weight.

These authors offered no explanation for their observation that very little neuromuscular blockade was produced in 2 of 45 patients in this study. The interesting observation was made that in all patients, neuromuscular blockade induced by succinylcholine was preceded by an increase in muscle tone. Marked increases in muscle tone occurred more frequently in neonates than in older children. There was also an increase in magnitude of the evoked contraction after recovery from paralysis induced by succinylcholine.[41]

A study using different methods of monitoring neuromuscular function[7] during unspecified anesthetic background, documented a similar potency of succinylcholine: ED_{95} = 445 μg/kg in children 1 to 4 years of age, 454 μg/kg in children 5 to 10 years of age, and 270 μg/kg in adolescents 11 to 15 years of age. This study supports the practice of administering 1 mg/kg of succinylcholine because the average degree of neuromuscular blockade induced was 99% in the 62 children between 1 and 15 years of age who received that dose. Onset appeared to be more rapid in the younger children although the differences were not statistically significant. Recovery to 50% of neuromuscular function did occur significantly sooner by about 5 minutes in the younger children, in an average of 3½ minutes, than in adolescents.[7]

Plumley and colleagues[57] evaluated the effects of succinylcholine in the presence of 2% inspired halothane in children between 3 and 10 years of age. They estimated that the ED_{95} of succinylcholine, for depression of twitch of the adductor pollicis, was 440 μg/kg. They also measured evoked twitch of the masseter simultaneously and observed more paralysis in the masseter than in the thumb. It might be expected that succinylcholine would be significantly more potent in the presence of halothane anesthesia than in the presence of nitrous oxide-thiopental-fentanyl anesthesia.[13] However, Meakin and colleagues[41] estimated that the ED_{90} dose of succinylcholine in children was 350 μg/kg. Thus, these two studies did not demonstrate any increase in the potency of succinylcholine in the presence of halothane.

Recently, it has been demonstrated that succinylcholine has effects that are counter to the facilitation of intubation. Studies of children anesthetized with halothane, enflurane, or isoflurane demonstrated that succinylcholine frequently produces an increase in tension of the masseter.[66–68] In 5 of the 76 children in whom movement of the thumb was completely abolished by succinylcholine, more than one attempt at intubation was required because of difficulty opening the mouth after succinylcholine administration.[66–68] In one of these patients, mouth opening, in response to a constant force of 1.7 newton, decreased from 20 mm to less than 1 mm after administration of succinylcholine (Figs. 1 and 2). Similarly, the mouth of one patient could not be opened following the administration of succinylcholine during isoflurane anesthesia.

Other investigators have observed a dose-related increase in resting tension in the masseter and the adductor pollicis that occurs during succinylcholine-induced paralysis in anesthetized children.[57, 58] The increase in resting tension of the masseter was of greater magnitude than that observed in the adductor pollicis. This increase in resting tension, or increased stiffness, of the masseter occurred when neurally evoked contraction of the muscle was abolished, i.e., in the presence of paralysis induced by succinylcholine. Administration of 0.05 mg/kg of curare 3 minutes

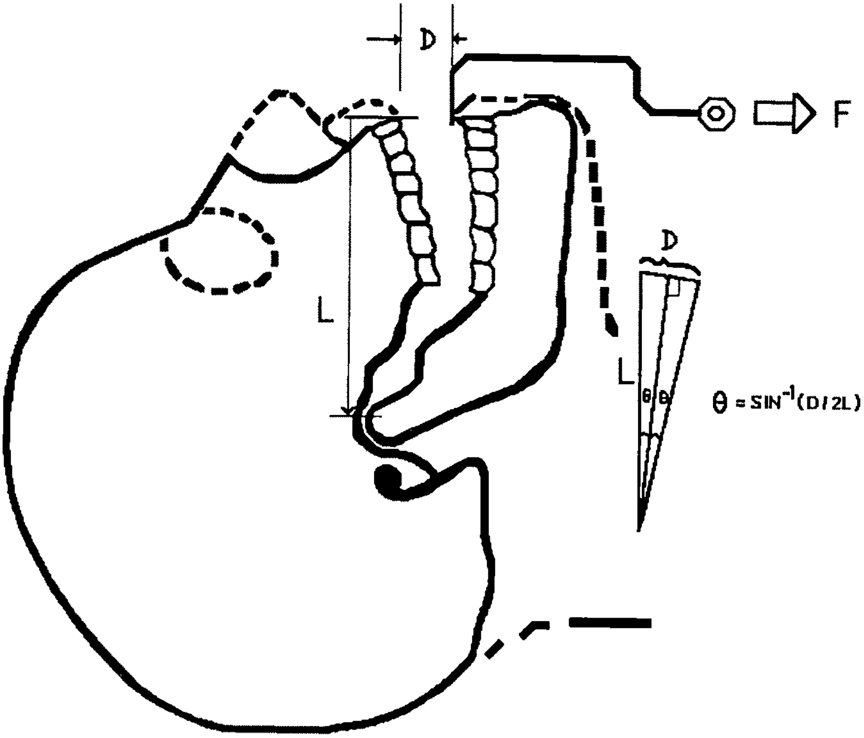

Figure 1. Schema of lateral view of face indicating the temporomandibular joint–to–incisor distance. (L), Incisor distance; (D), direction of the (F) constant force. (*From* Van Der Spek AFL, Fang WB, Ashton-Miller JA, et al: The effects of succinylcholine on mouth opening. Anesthesiology 67:459–465, 1987; with permission.)

before 1.0 mg/kg of succinylcholine did not prevent the increase in masseter muscle tension induced by succinylcholine in children anesthetized with halothane and nitrous oxide,[65] although it did prevent visible fasciculations.

These observations lend credence to retrospective chart reviews[8, 63] that claim that the incidence of masseter spasm in children anesthetized with halothane and then given succinylcholine is about 1%. Which of these children are susceptible to malignant hyperthermia is not easily determined.[35] In the study by Van Der Spek et al,[68] anesthesia was continued with the potent inhalation anesthetic used for induction in all patients without the appearance of signs of increased metabolic rate. In one case anesthesia was continued for 2½ hours with isoflurane.

Evaluation of postoperative serum creatine kinase concentrations after administration of succinylcholine in the presence of potent inhalation anesthetics, may not help to differentiate patients with muscle disease from those without. Recent observations of postoperative serum creatine kinase concentrations confirm earlier studies, which showed that subclinical damage to muscle is frequent in normal children who received halothane and succinylcholine. However, increases in serum creatine kinase concentrations measured 24 hours after surgery were less following administration of succinylcholine in the presence of thiopental and nitrous oxide, than in the presence of halothane and nitrous oxide.[40] The average increase in creatine kinase concentration was 247 U in the control group and about three times greater in the presence of halothane and succinylcholine. In addition, creatine kinase was more likely to increase after the administration of succinylcholine to

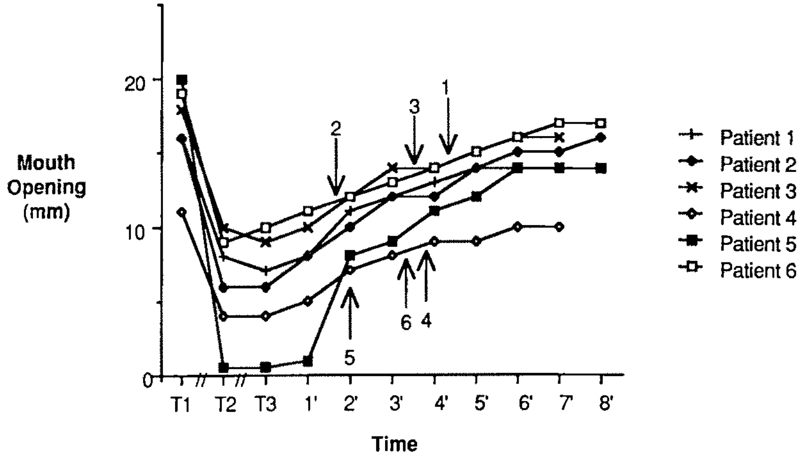

Figure 2. Mouth opening versus time. (*From* Van Der Spek AFL, Fang WB, Ashton-Miller JA, et al: Increased masticatory muscle stiffness during limb muscle flaccidity associated with succinylcholine administration. Anesthesiology 69:11–16, 1988; with permission.)

patients over 12 months of age than to younger infants.[10] As has been noted in earlier reports, postoperative creatine kinase concentration often increased after the administration of succinylcholine to patients with muscle disease, but not following similar anesthetics without succinylcholine.[33] But of what importance is a postoperative serum creatine kinase concentration of several thousand? This remains unclear. Such a patient may have entirely normal muscle and only a slightly exaggerated response to succinylcholine. Probably, most children with increased serum creatine kinase concentrations after exposure to halothane and succinylcholine would tolerate repeat anesthetics with halothane without any complication.

It is well known that hyperkalemia may occur after administration of succinylcholine.[30] Cases may occur in which the cause of succinylcholine-induced hyperkalemia cannot be definitely determined at the time, thus complicating management. Retrospectively, the likely causes of hyperkalemia may be somewhat clearer. Such was the case of succinylcholine-induced hyperkalemia in a 4-year-old boy with metastatic rhabdomyosarcoma[34] and that of succinylcholine-induced hyperkalemia in an infant presenting for inguinal herniorrhaphy.[14] Both of these patients required cardiac resuscitation because of hyperkalemia that followed the administration of succinylcholine. In the first case, it is speculated that the boy's history of 3 weeks of fever and malaise may have resulted in sufficient immobility to have altered the sensitivity of his muscles to succinylcholine or that the excessive potassium was released from the large metastatic mass of rhabdomyosarcoma present in the patient's bone marrow. In the second case, a diagnosis of Duchenne's muscular dystrophy was later confirmed by biopsy.

Nevertheless, succinylcholine remains the neuromuscular blocking drug with the most rapid onset of action and the shortest duration. During balanced anesthesia, succinylcholine can effectively facilitate rapid sequence intubation[11] with little chance of rigidity in the masseter.[37] Studies of the intubating conditions after administration of a muscle relaxant are somewhat difficult to interpret because as all practitioners appreciate, the ease of intubation is influenced by many factors, including the depth of anesthesia and degree of respiratory drive demonstrated by the patient. The timing of supplementary doses of intravenous (IV) drugs relative to attempted intubation of the trachea and the skill of the endoscopist are not usually reported. When the intubating conditions after administration of succinylcholine were compared with those after pancuronium in children from 2 to 8 years of age, during nitrous oxide-thiopental-droperidol-fentanyl anesthesia,[11] equally excellent conditions were obtained when either succinylcholine, 1.0 or 1.5 mg/kg, or pancuronium, 0.15 mg/kg, had produced 95% depression of twitch height of the adductor pollicis. It was necessary to wait 40 seconds longer for this degree of paralysis to develop following the administration of 0.15 mg/kg of pancuronium than after the administration of 1.5 mg/kg of succinylcholine. Because of the potential for complications and the diagnostic dilemmas that can ensue, anesthetists may prefer to administer a nondepolarizing neuromuscular blocker in lieu of succinylcholine when time allows.

NONDEPOLARIZING NEUROMUSCULAR BLOCKING DRUGS IN CLINICAL USE

Several recent studies have demonstrated significantly increased potency of nondepolarizing neuromuscular blocking drugs in young infants in comparison with older children. The potency of a drug administered by either bolus or infusion is influenced by the sensitivity of the tissue to the drug. The sensitivity of the tissue has been described by the plasma concentration of drug at which 50% depression of function occurs (Cpss_{50}). The potency of a drug administered by bolus is also influenced by the degree to which the drug is diluted in the body, i.e., the volume of distribution at steady state (VDSS). To account for differences in potency due to age-related changes in the volume of distribution, these muscle relaxants have been compared in a dose based on the dose of drug to surface area rather than to weight. This is based on the understanding that the volume of distribution of the drug changes as both the extracellular fluid volume and the surface area to weight ratio change during growth and development. When pharmacokinetic studies examine neuromuscular blocking drugs in pediatric patients, a uniform finding is that VDSS in milliliters per kilogram, and in milliliters per square meter, is greater in the infant than the child. Although there may be age-related changes in volume of distribution of some drugs between children, adolescents, and adults, this does not always hold true, as evidenced by vecuronium.[18]

An increase in potency might be expected to be accompanied by an increase in duration of action. Such has not always been observed. In fact, age-related differences in recovery from neuromuscular blockade may be attributed to age-related differences in clearance of the neuromuscular blocking drugs secondary to changes in the function of excretory pathways, including plasma esterases and to age-related differences in the removal of the drug from its site of action. In the final analysis, for a model of drug effect to be useful for the clinician, it must explain clinical observations.

Atracurium

The most carefully age-stratified studies of the potency of atracurium are those of Meretoja and Wirtavuori.[48] These investigators found atracurium to be significantly more potent in infants of less than 1 year of age (more precisely in infants of less than 6–8 months of age) than in children between 3 and 12 years of age (Table 1) during nitrous oxide-barbiturate-fentanyl anesthesia. When these investigators referenced the dose of atracurium to body surface area rather than to weight, the difference in potency became even more apparent. They found that atracurium was about twice as potent in patients less than 1 year of age than it was in patients 1 to 16 years of age. Similar age-related differences in the potency of atracurium during balanced anesthesia have been documented using other methods of monitoring and dose-response determinations.[42] These results are consistent with one earlier study[5]

Table 1. *Changes in the Potency of a Bolus of Atracurium with Age* ($\bar{X}$ ± *SEM*)

AGE	ED_{95} (μg/kg^{-1})
<1 mo	217 ± 18
1–3 mo	234 ± 23
3–12 mo	229 ± 22
1–3 yr	310 ± 26
3–5 yr	322 ± 15
5–8 yr	324 ± 19
8–12 yr	330 ± 15
12–16 yr	300 ± 20

Data were collected during nitrous oxide-barbiturate-narcotic anesthesia. See text for discussion of significance.

Adapted from Meretoja OA, Wirtavuori K: Influence of age on the dose-response relationship of atracurium in paediatric patients. Acta Anaesthesiol Scand 32:615, 1988; with permission.

performed during halothane anesthesia, which also found that the potency of atracurium in milligrams per square meter was almost twice as great in infants as in children or adolescents. A study that differed in that force transduction rather than electromyography was employed for monitoring found no age-related changes in atracurium potency, referenced to body weight, during halothane anesthesia.[25]

The recent study by Meakin and colleagues[42] demonstrated a more rapid recovery to 10% of control neuromuscular function from a bolus of 0.5 mg/kg in neonates in comparison with infants of more than 6 weeks of age and children up to 5 years of age. Similarly, more rapid recovery in younger patients was also noted in the earlier observations of infants during halothane anesthesia.[5] In both cases, although infants were more sensitive to atracurium, they recovered more rapidly from its effects than did older patients. There is a case report[9] of the administration of 80 times the ED_{95} of atracurium administered over 30 minutes by infusion pump to a 2-month-old infant. The child was flushed, but not hypotensive and recovered fully about 2½ hours after the infusion was discontinued.

Age-related differences in onset of paralysis with atracurium have been documented. Younger patients are paralyzed significantly more rapidly than older patients. A bolus of 0.5 mg/kg of atracurium depresses 95% twitch height in the thumb in an average of 0.9 minutes in neonates and 1.4 minutes in children during nitrous oxide-thiopental-fentanyl anesthesia.[42] Although this age-related difference in onset could be due in part to the age-related difference in potency, and hence the administration of a more potent dose to the younger patient, the more rapid recovery from the large dose suggests that redistribution of drug in the younger patient may also contribute to the observed effects. A combined pharmacokinetic and pharmacodynamic study could address these issues.

The only combined pharmacokinetic and pharmacodynamic study of atracurium[17] was performed during nitrous oxide-halothane anesthesia. It demonstrated that the volume of distribution at steady state (VDSS in milliliters per kilogram) and total clearance of atracurium decreased significantly with increasing age from infancy to adulthood. However, neither the plasma concentration at which 50% depression of neuromuscular function occurred ($CPSS_{50}$), nor the rate constant for equilibration of drug between the blood and the effect site ($t_{1/2}keo$), nor the elimination half-life of atracurium, changed significantly with age. Thus, the results of this study differ from those of the earlier studies of vecuronium[18] and D-tubocurarine,[20] which demonstrated significantly lower $CPSS_{50}$ in the infant in comparison with the older patient. It has been argued that the dose requirement of these drugs should be determined by the the product of VDSS and $CPSS_{50}$.[20]

Therefore, the results of this study of atracurium do not explain the increased sensitivity of the infant to atracurium administered by bolus, which has been repeatedly observed by other investigators. Perhaps methodologic differences in monitoring or the relatively small number of older infants (six infants between the ages of 4 and 11 months) in the pharmacodynamic study are responsible for this discrepancy.

Clinically oriented studies may answer clinically useful questions if the population studied is carefully described. Thirty children between the ages of 2 and 10 years of age were anesthetized with halothane. No premedication was administered. Nitrous oxide, 60% inspired, and halothane were administered. The concentration of halothane was gradually increased to 1.5% inspired and continued at that concentration for 15 minutes. Although these authors[69] do not describe their method of monitoring neuromuscular function other than to say that supramaximal stimuli were delivered to the ulnar nerve as a train-of-four stimuli at 10-second intervals, one presumes that monitoring must have been quantitative because the authors claimed that the tracheas were intubated when neuromuscular function was depressed by 80%. It is not at all surprising that this should be easy to accomplish after 15 minutes of adequate ventilation with 1.5% halothane. Nevertheless, it is worth noting that the time from injection of atracurium to 25% recovery of neuromuscular function (T_{25}) was about 24 minutes after 0.25 mg/kg of atracurium and about 33 minutes after 0.4 mg/kg.

Sixty-seven children between 1 and 8 years of age were anesthetized with IV thiopental followed by nitrous oxide-halothane 1.5% inspired for 10 to 20 minutes before administration of one of four drugs.[53] With electromyographic monitoring at a stimulus frequency of a train-of-four every 20 seconds, there was no significant difference between time to maximum paralysis following the administration of 0.4 mg/kg of atracurium, 0.8 mg/kg of D-tubocurarine, 0.12 mg/kg of pancuronium, or 0.07 mg/kg of vecuronium. The times from drug administration to recovery of 25% of neuromuscular function were greater than 60 minutes for pancuronium and D-tubocurarine, about 38 minutes for atracurium, and about 26 minutes for vecuronium.

In children who had been burned more than 7 days previously, the potency of atracurium was significantly decreased.[51] As the percentage of the body surface area involved by the burn increased, the resistance to atracurium increased. When more than 60% of the surface area was burned, the potency of atracurium was ten times less than in normal patients or in those who had burns just as extensive but that occurred less than 7 days previously. These findings are similar to those noted by Martyn in previous studies of D-tubocurarine in adults.

The pharmacokinetic and pharmacodynamic study by Fisher et al[17] claims that the infusion rate of atracurium required at steady state to produce a constant degree of depression of neuromuscular function in infants should be similar to that in children. Clinical studies of atracurium infusion rates in infants and children[27, 29] during halothane anesthesia have demonstrated no statistically significant age-related difference with the average infusion requirements being 7.6 ± 0.3 and 8.3 ± 0.4 μg/kg/min (X ± SEM), respectively, to maintain about 95% depression of neuromuscular function during 1% inspired halothane. These studies are remarkable for the large degree of variability in effective infusion rate both within and between individuals. During nitrous oxide-barbiturate-fentanyl anesthesia, Kalli and Meretoja[32] also observed no significant difference in effective infusion rates of atracurium in milligram per kilogram, in patients from 1 month to 17 years of age. The effective rate was about 0.5 mg/kg/h or 8 μg/kg/min. However, the effective atracurium infusion rate in mg/kg/h was 25% lower in neonates, i.e., in patients less than 1 month old (Table 2). It would appear from these recent studies that unidentified differences between populations or in methods obscure the potentiation

Table 2. *Changes in the Potency of an Infusion of Atracurium with Age ($\bar{X}$ ± SEM)*

AGE (yr)	WEIGHT (kg)	IR_{90-95} (μg/kg^{-1})	IR_{90-95} (μg/kg^{-2}/h)
0.3 ± 0.1	4.2 ± 0.2	0.44 ± 0.04	7.41 ± 0.71
0.6 ± 0.1	5.8 ± 0.2	0.52 ± 0.04	9.65 ± 0.76
1.3 ± 0.1	8.4 ± 0.3	0.53 ± 0.02	10.78 ± 0.30
2.8 ± 0.4	12.6 ± 0.5	0.50 ± 0.03	11.44 ± 0.64
6.1 ± 0.4	16.9 ± 0.5	0.52 ± 0.05	12.46 ± 1.13
8.2 ± 0.5	24.1 ± 0.9	0.54 ± 0.02	14.15 ± 0.58
13.3 ± 0.8	44.1 ± 3.8	0.56 ± 0.04	17.42 ± 1.27

Data were collected during nitrous oxide-barbiturate-narcotic anesthesia. See text for discussion of significance.

Adapted from Kalli I, Meretoja OA: Infusion of atracurium in neonates, infants and children: A study of dose requirements. Br J Anaesth 60:651, 1988; with permission.

of atracurium-induced neuromuscular blockade by halothane, which was noted by previous investigators.[3]

When the infusion rate of atracurium was referenced to surface area rather than weight, age-related differences in infusion requirement became more apparent.[32] Neonates weighing less than 5 kg were significantly more sensitive than children over 12 months of age who weighed more than 10 kg, and almost twice as sensitive as 8-year-old children weighing more than 30 kg. Toddlers less than 10 kg were significantly more sensitive to an infusion of atracurium than were older children weighing more than 20 kg (Table 2). A significant correlation was found between the infusion rate of atracurium in milligram per meter squared per hour and the logarithm of body surface area ($y = 12.2 \log$ body surface area $+ 15.1$, $n = 75$, $r = 0.76$, $P = 0.001$).

Whether atracurium is administered as a bolus or an infusion, it may be advantageous to the patient that the rate of recovery from the drug is relatively rapid. In most clinical practice, monitoring of neuromuscular function is subjective. When neuromuscular blockade was maintained at 85% to 95%, one to two twitches in a train-of-four, with atracurium during surgery performed in the presence of nitrous oxide-narcotic-barbiturate anesthesia, neostigmine, 50 μg/kg, administered at the end of surgery, and the endotracheal tube removed when spontaneous ventilation and muscle power were judged to be clinically adequate, the train-of-four ratio was likely to be greater than 0.75 when the patient arrived in the recovery area.[45] When the effects of a neuromuscular blocking drug with longer duration of action were observed under the same circumstances, although the train-of-four ratio was similar at the time of extubation (about 0.5), the time that passed until neuromuscular function recovered to the same degree was significantly longer by 10 to 15 minutes. No matter what degree of neuromuscular function was present when anticholinesterase was administered, the time from administration of neostigmine to recovery of the train-of-four ratio to greater than 90% was shorter when atracurium rather than a drug (alcuronium) with a longer expected duration of action was present. As had been noted in the presence of vecuronium,[43] the greater the degree of spontaneous recovery of neuromuscular function at the time of administration of anticholinesterase, the more rapid the recovery of neuromuscular function.[45]

Vecuronium

The dose-response relationship of vecuronium appears to be somewhat more age dependent than that of atracurium. During nitrous oxide-thiopental-fentanyl anesthesia the potency of vecuronium, in milligram per kilogram, was significantly greater in infants less than 2 years old than in children between the ages of 2 and 10 years, and greater in adolescents than in children (Table 3). Whether dosing was referenced to weight or surface area, vecuronium was about twice as potent in infants as in children over the age of 2 years. When the dose of vecuronium was referenced to body surface area rather than to weight, there was no significant difference in potency between children and adolescents. These findings differ from those of an earlier dose-response study of vecuronium during halothane anesthesia, which found no significant difference in potency of vecuronium with age from 7 weeks to 38 years.[19]

There was more age-related variation in the duration of action of vecuronium. The rate of recovery of neuromuscular function was about 50% slower in infants than in children. After a dose of 100 μg/kg of vecuronium during nitrous oxide-thiopental-fentanyl anesthesia, greater than 90% neuromuscular blockade persisted for an average of 58 minutes in infants, 18 minutes in children, and 37 minutes in adolescents.[49] Similar differences in rate of recovery from vecuronium have been observed during halothane anesthesia.[19] These marked age-related differences in rate of recovery from vecuronium in comparison with atracurium could be due to either more marked changes in potency of the drug with age, or to more marked pharmacokinetic differences with age. There has been only one study that attempted to separate these factors.[18] This study, performed during halothane anesthesia, demonstrated a significantly decreased CPSS_{50} in infants of 3 to 11 months of age in comparison with children over 1 year of age and adults, and a significantly larger VDSS in infants in comparison with children. There was no significant difference in VDSS or clearance of vecuronium between children and adults in this study. Neither was there a statistically significant difference in $t_{1/2}$keo with age in this study. Nevertheless, the calculated differences in CPSS_{50} and VDSS between infants and children are consistent with the observed increased duration of action of vecuronium in the infant. When the dose of vecuronium administered as a bolus is increased to 0.4 mg/kg in healthy children from 2 to 8 years of age, during nitrous oxide-narcotic-sedative anesthesia, the time to onset of effect was about 40 seconds.[64] This compares with an onset time of about 20 seconds for succinylcholine, 2 mg/kg, under the same conditions. These two times were not statistically significantly different;

Table 3. *Changes in the Potency of Vecuronium with Age* ($\bar{X}$ ± *SEM*)

AGE	ED_{95} (μg/kg^{-1})	$\mathrm{IR}_{90\text{-}95}$ (μg/kg^{-1}/hr^{-1})
<1 month	48 ± 4	—
1–3 months	44 ± 4	62 ± 19
3–12 months	49 ± 3	62 ± 12
1–2 years	57 ± 5	94 ± 18
2–3 years	72 ± 5	128 ± 29
3–5 years	80 ± 4	149 ± 33
5–7 years	82 ± 5	162 ± 59
7–10 years	81 ± 4	150 ± 56
10–13 years	71 ± 4	124 ± 42
13–16 years	55 ± 4	89 ± 13

Data were collected during nitrous oxide-barbiturate-narcotic anesthesia. See text for discussion of significance.

Adapted from Meretoja OA, Wirtavouri K, Neuvonen PJ: Age-dependence of the dose-response curve of vecuronium in pediatric patients during balanced anesthesia. Anesth Analg 67:21, 1988; and Meretoja OA: Vercuronium infusion requirements in pediatric patients during fentanyl-nitrous oxide-oxygen anesthesia. Anesth Analg 68:20, 1989; with permission.

however, they were different from the longer onset times that followed the administration of lower doses of vecuronium. In comparison, the dose of 0.1 mg/kg of vecuronium had an onset time of about 2 minutes, and T_{25} occurred about 24 minutes after maximal depression of neuromuscular function. As the dose of vecuronium increased so did the time from maximal effect to T_{25}, and so did the rate of recovery as measured by the time from 25% to 75% recovery of function, T_{25-75}. These were about three times larger or longer after 0.4 mg/kg of vecuronium than after 0.1 mg/kg.[64] Thus, vecuronium becomes a "long-acting" neuromuscular blocking drug in children when it is administered in doses large enough to produce paralysis as rapidly as does succinylcholine.

In children from 6 months of age to 17 years of age who had been burned more than 7 days previously, the potency of vecuronium was significantly decreased.[52] As the percentage of the body surface area involved by the burn increased, the resistance to vecuronium increased. When 40% to 60% of the surface area was burned, about three times more vecuronium was required than in normal patients. When more than 60% of the surface area was burned, even 15% more was required. Previously burned patients had a normal response to the drug 3 years after the injury.

When repeated doses or infusions of vecuronium were administered there was a marked difference in response at different ages that was similar to the differences in potency of a bolus dose. Referenced to body surface area, the effective infusion rate of vecuronium in neonates was 25% to 30% of that in children over the age of 2 years, and children and adolescents required similar infusion rates[50] (see Table 3). Referenced to body weight, the effective infusion rate of vecuronium in neonates was 30% to 50% of that in children over the age of 2 years, and adolescents required significantly less than did children. The relative sensitivity of the infant to an infusion of vecuronium is consistent with the results of dose-response and pharmacodynamic studies of this drug. During nitrous oxide-barbiturate-narcotic anesthesia, the hourly dose of vecuronium required to maintain 95% depression of neuromuscular function is about 200% of the ED_{95} in children and adolescents, but only 140% to 170% of the ED_{95} in infants.[50] The effective vecuronium infusion rate in children is significantly greater than that in adults exposed to similar anesthetics.[15] These observations might suggest that the clearance of vecuronium is significantly faster in children in comparison with adolescents and adults. This has not been documented by pharmacokinetic studies.

In the intensive care unit when patients are monitored with a visual assessment of the train-of-four response and drug administered when a fourth response is observed, administration of vecuronium by infusion may be useful. With a crossover design, vecuronium was administered either by hourly bolus or constant infusion.[16] The dose per weight was significantly less, averaging a total of 0.79 mg/kg over 12 hours, with a range of 0.1 to 1.8 mg/kg when vecuronium was administered as an infusion. When vecuronium was administered as hourly boluses, the average dose was a total of 1.34 mg/kg, with a range of 1 to 2.55 mg/kg over 12 hours.

A study of the relative effects of different anesthetics on the potency of vecuronium was performed by Pittet and colleagues[54] in children from 2 to 9 years of age. These investigators found that the ED_{95} of vecuronium during nitrous oxide-thiopental-alfentanil anesthesia was 70 μg/kg, similar to the potency of vecuronium previously observed during anesthesia including fentanyl rather than alfentanil. Isoflurane (1.2% end-tidal) and halothane (0.7% end-tidal) both potentiated vecuronium, producing ED_{95}s of 42 and 47 μg/kg, respectively. Initial recovery from paralysis, the time from maximal initial effect to 25% recovery of function, was not significantly different during the different anesthetic conditions. However, the average time from 25% to 75% recovery, T_{25-75}, was significantly longer in the presence of isoflurane (13 minutes) than in the presence of halothane (8 minutes) or in the absence of potent inhalation anesthetics (9 minutes). The potentiation of vecuronium by isoflurane and by halothane demonstrated by Pittet and colleagues is similar to that observed during infusion of vecuronium.[15]

The question of the effect of timing of administration of neostigmine for the purpose of induction of recovery from vecuronium-induced neuromuscular blockade was addressed during halothane-nitrous oxide anesthesia in children.[43] The elapsed time from the beginning of spontaneous recovery of neuromuscular function, when the first response to the train-of-four stimuli was 1% of baseline, to the return of the first response of the train-of-four to 90% of baseline was similar whether 30 μg/kg of neostigmine was administered when the initial response was 1%, 10%, or 25% of baseline. However, there was a significant difference in the train-of-four ratio 10 minutes after the administration of neostigmine. Those patients who had received 30 μg/kg of neostigmine when spontaneous recovery was only 1% did not all have train-of-four ratios greater than 0.75 even 12 minutes after administration of anticholinesterase. This study demonstrates that when an appropriate dose of anticholinesterase is administered during paralysis with vecuronium when only a slight, single response to a train-of-four stimuli can be observed, residual paralysis can be documented frequently within the period of time in which the anesthetist could be expected to transfer care of the patient. However, if neostigmine was administered when neuromuscular function had returned to 10% of initial baseline after bolus administration of vecuronium, patients of all ages from infancy to adulthood recovered a train-of-four ratio of 0.7 within 10 minutes.[12]

Pancuronium and D-Tubocurarine

The earlier studies of the dose-response relationships of nondepolarizing drugs with longer durations of action, pancuronium, D-tubocurarine, and metocurine, found no significant difference in potency with age in the range from the first week through 7 years.[24, 26, 28] These studies were performed with force transduction monitoring during halothane anesthesia. Reexamination of the potency of pancuronium during halothane anesthesia, using electromyography, has demonstrated an increased potency of pancuronium, in milligram per kilogram, in infants of 3 to 6 months of age in comparison with children over 1 year of age.[2] In this study the young infants required about 30% less pancuronium (ED_{95} = 45 μg/kg) than did the children (ED_{95} = 62 μg/kg) to produce 95% depression of neuromuscular function. When the dose was referenced to surface area rather than to weight, infants required 60% less than did children over the age of 4 years.

During nitrous oxide-thiopental-fentanyl anesthesia significant age-related differences in potency of pancuronium have been documented.[46] The dose of pancuronium, which produced 95% depression of neuromuscular function was 30% to 35% less in infants (ED_{95} = 66 mg/kg) than in children (ED_{95} = 93 mg/kg) and 15% to 20% less in adolescents (ED_{95} = 77 mg/kg) than in children. Laycock et al[36] found a similar difference in potency of pancuronium between infants and children. When ED_{95} was calculated on the basis of surface area, the difference between children and adolescents disappeared (ED_{95} = 2.5 mg/m²), and infants were almost twice as sensitive as the older patients (ED_{95} = 1.4 mg/m²). However, as had been noted previously in a study of D-tubocurarine,[39] there was one neonate who was markedly resistant to pancuronium (ED_{95} = 123 μg/kg) for no apparent reason.

Although pancuronium was more potent in the younger infants when the drug was administered incrementally to produce greater than 85% depression of neuromuscular function, there was no difference in the initial rate of recovery in patients from 3 months to 6 years of age during halothane anesthesia,[2] or in patients from 1 day to 16 years of age during nitrous oxide-narcotic anesthesia.[46]

Similarly the potency of D-tubocurarine was about 25% greater in infants (ED_{95} = 414 μg/kg) than in children (ED_{95} = 499 μg/kg).[44] Adolescents observed under the same conditions, diazepam premedication, thiopental, and nitrous oxide anesthesia, had an ED_{95} = 445 μg/kg. Although these age-related changes in potency of D-tubocurarine are similar to those documented for other drugs, there was greater interindividual variability in these studies, and the differences between the age groups were not statistically significant.

There are changes in the potency of these drugs that have been recently documented related to disease states in pediatric patients. Peculiar resistance to D-tubocurarine, and to a lesser extent alcuronium, has been noted in some children with malignancies, especially those of the liver, kidney, or bone.[6] The reason for slowed onset of effect and hence larger initial dose requirement is not known. However, after successful treatment, the patients' neuromuscular response returned toward normal. In pediatric patients 5 to 10 years after acute poliomyelitis, there was a significant increase in potency of pancuronium (ED_{50} = 29 μg/kg versus 41 μg/kg in the normal patients)[31] in upper extremities that had not been affected by the disease. Response to D-tubocurarine was similar, ED_{50} = 0.115 mg/kg in patients who had had polio, and 0.203 mg/kg in normal patients.

The dose-response relationship of pancuronium was documented in identical twins[21] and clinically identical anesthetic and monitoring conditions. The twins weighed 11 and 11.5 kg and were anesthetized within 45 minutes of each other. The ED_{50} of twin A was 19.5 μg/kg, while the ED_{50} of twin B, the more physically active infant, was 27 μg/kg. These values are within the expected normal range in infants. It would appear that the inherent variability in dose-response observations is independent of genetic qualities.

Pipecuronium

Pipecuronium, a steroidal neuromuscular blocking drug similar to pancuronium, has recently been made available for clinical use in North America. Pipecuronium appears to be similar to other steroidal neuromuscular blocking drugs in that there are age-related differences in its potency. During nitrous oxide-fentanyl anesthesia, pipecuronium was about 40% less potent on a weight basis in children than in adults.[56] There was no statistically significant difference in rate of recovery from pipecuronium with age although the T_{25-75} was 33 ± 5 minutes (X ± SEM) in adults and 23 ± 1 minutes in children during nitrous oxide-fentanyl anesthesia. In children the T_{25-75} was significantly prolonged by isoflurane anesthesia. In addition, there was a significant difference in potency of pipecuronium, as defined by the ED_{50}, in children during exposure to different anesthetics. The ED_{50} of pipecuronium was 44 μg/kg during nitrous oxide-fentanyl anesthesia, 23 μg/kg during exposure to isoflurane (1.2% end-tidal), and 33 μg/kg during exposure to halothane (0.7% end-tidal).[56]

There appeared to be no difference in the potency of pipecuronium in children when alfentanil replaced fentanyl in the anesthetic.[55] During nitrous oxide-alfentanil anesthesia there were significant age-related differences in potency and duration of action of pipecuronium in pediatric patients. The potency of pipecuronium in infants less than 1 year of age was about 30% greater than its potency in children more than 2 years of age. Although the T_{25-75} was similar in infants and children, early recovery rate, i.e., the time from 10% to 25% recovery of function, T_{10-25}, was significantly faster in patients less than 1 year of age than in older children.

As would be expected, the potency of pipecuronium during halothane anesthesia,[61] in microgram per kilogram, was 25% greater in infants 3 to 6 months of age than in children over 3 years of age. The respective ED_{50}s were 18 and 24 μg/kg. When the drug dose was referenced to body surface area rather than body weight, age-related differences in potency became more apparent; 3- to 6-month-old infants were about 30% more sensitive than children of over 1 year of age, and infants of 6 to 12 months were about 25% more sensitive than children 3 to 6 years of age. This study also noted that when the dose of pipecuronium had been titrated to produce at least 90% blockade of neuromuscular function, the time required for spontaneous recovery to progress from 10% to 25% was statistically significantly less in 3- to 6-month-old infants in comparison to 1- to 3-year-old children. However, the difference was small and there was no significant difference in the T_{25-75} between age groups. The average T_{25-75} was 25 to 30 minutes for pipecuronium in these infants and children anesthetized with halothane.

The onset and duration of action of larger doses of pipecuronium in pediatric patients have not been documented.

NONDEPOLARIZING NEUROMUSCULAR BLOCKING DRUGS UNDERGOING CLINICAL TRIALS IN 1990 AND 1991

Doxacurium

Doxacurium, a benzylisoquinolinium neuromuscular blocking drug, is being evaluated by the Food and Drug Administration in 1991. The two published studies of this drug have remarkably similar results (ED_{50} = 19 μg/kg in both studies, ED_{95} = 27 or 32 μg/kg), although one[60] was performed with electromyographic monitoring and the other was performed with the classic force transduction monitoring.[23] Both studies were performed in children between 2 and 12 years of age during halothane anesthesia (1% inspired or 0.8% end-tidal). Thus, doxacurium is similar to many other nondepolarizing neuromuscular blocking drugs in that its potency in children during nitrous oxide-halothane anesthesia is very similar to its potency in adults during nitrous oxide-narcotic anesthesia. In these two studies together 17 patients received 50 μg/kg of doxacurium. All of these patients developed greater than 95% depression of neuromuscular function. Doxacurium produced completed paralysis in 14 of these patients. The time required for maximal blockade to develop after the administration of 50 μg/kg of doxacurium averaged 5 to 6 minutes.

Doxacurium is a long-acting drug in that the duration of greater than 75% depression of neuromuscular function after 50 μg/kg averages 44 to 51 minutes. The T_{25-75} recovery time averages 25 to 35 minutes at any of the doses that have been studied to date. Therefore, the neuromuscular effects of doxacurium are similar to those of pipecuronium or pancuronium. Further comparison between these drugs awaits the study of doxacurium during other types of anesthesia in infants and in pediatric patients with excretory failure.

Mivacurium

Mivacurium, another benzylisoquinolinium neuromuscular blocking drug, is also being evaluated by the Food and Drug Administration in 1991. This drug is much different from the other nondepolarizing neuromuscular blocking agents in the timing of its neuromuscular effects because it is metabolized by pseudocholinesterase (plasma cholinesterase or butyrylcholinesterase).

The potency of mivacurium in children and adults differs significantly. During nitrous oxide-narcotic anesthesia, children required 50% more mivacurium in milligrams per kilogram than did adults to produce the same degree of neuromuscular blockade. The respective ED_{50}s were 62 μg/kg and 43 μg/kg.[62] This difference in potency was abolished if the dose was referenced to surface area rather than to weight. The ED_{50} in children was 1558 μg/m^2, and the ED_{50} in adults was 1752 μg/m^2. The other dose-response study, which employed force-transduction monitoring rather than electromyography, demonstrated similar potency of mivacurium in children during nitrous oxide-narcotic anesthesia (ED_{50} of 59 μg/kg).[22] The ED_{50}s of mivacurium documented during halothane anesthesia, 1% inspired or 0.8% end-tidal, were 51 μg/kg[22] and 52 μg/kg,[62] respectively. Thus, there was possibly a slight degree of potentiation of the neuromuscular effects of mivacurium in the presence of halothane. This effect was so small that it reached statistical significance in only one[62] of these two studies.

The most noteworthy effects of mivacurium were that when it was administered in doses that might be used to facilitate intubation, 200 to 250 μg/kg, complete neuromuscular blockade was produced in an average of 1 to 2 minutes, and recovery to 25% of initial neuromuscular function occurred in an average of 7 to 14 minutes, depending on dose and anesthetic background. There was significant age-related variation in these effects of mivacurium in that when given in equipotent doses, both onset and recovery occurred more rapidly in the child than in the adult (Table 4). Thus, mivacurium could facilitate intubation of the trachea in children within a period of time that would be acceptable for many circumstances in the practice of pediatric anesthesia, and it could allow rapid recovery of neuromuscular function in patients with normal function of pseudocholinesterase. The T_{25-75} averaged between 3 and 5 minutes in these two studies. In children anesthetized with halothane, neuromuscular function returned to 95% of the baseline and the fourth response in the train-of-four was greater than 75% of the initial response 15 to 30 minutes after the administration of a bolus of 250 μg/kg of mivacurium. Therefore, if mivacurium were administered only to facilitate intubation in a child with normal neuromuscular function and normal pseudocholinesterase activity, and the duration of surgery was greater than 30 minutes, there would be little need to administer anticholinesterase, and the potential for residual neuromuscular blockade after termination of anesthesia would be lessened in comparison to the potential residual blockade following the administration of other nondepolarizing drugs.

Administration of mivacurium has been followed by the appearance of cutaneous flushing of the face and torso, which is thought to be due to histamine release. Such flushing was observed in 3 of 18 patients who received 250 μg/kg of mivacurium

Table 4. *The Effects of Mivacurium During Narcotic-Nitrous-Oxide Anesthesia in Children and Adults* ($\bar{X}$ ± *SEM, range)*

		RECOVERY†		
	ONSET* (min)	*T5 (min)*	*T25 (min)*	INFUSION RATE‡ ($\mu g/kg^{-1}/min^{-1}$)
Children	1.6 ± 0.1	6.8 ± 0.8	9.1 ± 0.9	15.6 ± 0.8
0.25 mg/kg	(1.0–2.2)	(3.7–9.3)	(4.8–12.0)	(7.8–31.4)
N	8	8	8	38
Adults	2.9 ± 0.3	13.5 ± 0.8	17.3 ± 1.8	6.4 ± 0.6
0.20 mg/kg	(1.8–4.5)	(9.8–18)	(9.9–34)	(2.7–10.4)
N	13	13	13	17

*Onset = time from injection to complete paralysis.

†Recovery to T_5 = time from injection to recovery of 5% of neuromuscular function; recovery to T_{25} = time from injection to recovery of 25% or three responses to a train-of-four stimuli.

‡Infusion rate = rate required to produce 89% to 99% neuromuscular blockade.

Data from Brandom BW, Sarner J, Woelfel SK, et al: Mivacurium infusion requirements in pediatric surgical patients during nitrous oxide-halothane and during nitrous oxide-narcotic anesthesia. Anesth Analg 71:16, 1990; Sarner JB, Brandom BW, Woelfel SK, et al: Clinical pharmacology of mivacurium chloride (BW B1090U) in children during nitrous oxide-halothane and nitrous oxide-narcotic anesthesia. Anesth Analg 68:116, 1988; and Weber S, Brandom BW, Powers DM, et al: Mivacurium chloride (BW B1090U)-induced neuromuscular blockade during nitrous oxide-isoflurane and nitrous oxide-narcotic anesthesia in adult surgical patients. Anesth Analg 67:495, 1988.

by rapid IV bolus.[62] In one of these patients hypertension occurred, probably due to concurrent tracheal intubation. In the other two patients there was a decrease in mean arterial blood pressure by 10% and 32% of the baseline immediately before drug administration. This hypotension resolved spontaneously within 2 minutes. Considering all nine patients who received 250 μg/kg of mivacurium, there was no significant change in heart rate or blood pressure with time. Of the 90 patients observed by a different group of investigators,[22] three manifested cutaneous reactions to mivacurium. One patient developed maculopapular redness along the vein through which mivacurium was being administered when the blood pressure cuff was inflated on the same arm. Another patient developed a mild flush after the administration of 100 μg/kg of mivacurium, as a second dose of the drug. The third patient developed a maculopapular rash over the chest and neck and mild transient hypotension after administration of 200 μg/kg of mivacurium. The cardiovascular effects of higher doses of mivacurium have not been examined in children. It is likely that the same recommendations for method of administration of drug that have served to minimize these effects with other neuromuscular blocking drugs will also decrease the incidence of cutaneous reactions and transient hypotension following the administration of mivacurium.

Because the duration of action of mivacurium is so short, it might be usefully administered as an infusion much the way in which succinylcholine has been administered, but without the problems of tachyphylaxis and phase 2 blockade. There have been two studies of mivacurium administered in such a manner to children anesthetized with nitrous oxide-narcotic with or without halothane.[1,4] Both studies found a three- to fourfold variation between patients in the average infusion rate of mivacurium required to maintain 95% depression of neuromuscular function (infusion requirement). It would appear that this degree of neuromuscular blockade can be produced by an average of 13 to 16 μg/kg/min of mivacurium during nitrous oxide-narcotic anesthesia in children. When halothane (1% inspired or 0.8% end-tidal) is added to the anesthetic the infusion requirement of mivacurium is somewhat less, an average of 10 to 12 μg/kg/min, respectively. Although one study[1] found no relationship between plasma cholinesterase activity and mivacurium infusion requirement, the other study[4] found that plasma cholinesterase activity, even in the normal range, was more significant than the presence of halothane in determining the infusion requirement of mivacurium. When considering the infusion requirement of mivacurium in micrograms per kilogram per minute, age, between 2 and 10 years, was also a more significant factor than was the presence of halothane.[4] However, when infusion requirement was referenced to body surface area rather than to weight, age was no longer important. The mivacurium infusion requirement was 375 ± 19 μg/m^2/min during nitrous oxide-narcotic anesthesia in children and 315 ± 26 μg/m^2/min when halothane (0.8% end-tidal) was also part of the anesthetic. The rate of recovery from mivacurium-induced neuromuscular blockade was the same after a single bolus and after infusions. The longest duration of infusion of mivacurium documented in a child was 294 minutes. In children, referencing mivacurium infusion requirement to body surface area rather than to weight eliminated age as an important predictor of infusion requirement. However, a difference between children and adults remains when the infusion requirement for adults is referenced to surface area. The infusion requirement for adults during nitrous oxide-narcotic anesthesia is 250 μg/m^2/min or less. The differences between these populations or the methods of the studies involved that may contribute to this difference in mivacurium infusion requirement have not been determined.

Documentation of the effects of mivacurium in infants and toddlers from 2 months to 2 years of age has begun. In early 1991 there were insufficient data to make any definitive statement about the relative potency of mivacurium in this age group. However, it appears likely that mivacurium will have at least as short a duration of action in infants as it has been shown to have in children.

ORG 9426

ORG 9426 is a steroidal neuromuscular blocker with lower potency than vecuronium and a similar lack of cardiovascular effects. The potency of 9426 has been documented by a study of more than 60 children from 1 to 5 years of age. During nitrous oxide-halothane (0.8% end-tidal) anesthesia the ED_{50} was about 180 μg/kg, and the ED_{95} was about 300 μg/kg.[71] These authors observed about fourfold resistance to 9426 in one patient during the initial loading period when hypertension and tachycardia were marked. These cardiovascular changes were thought to be the result of neosynephrine nose drops administered after atropine had been administered IV. Following nasotracheal intubation heart rate and blood pressure returned to baseline and the patient did not exhibit resistance to an infusion of 9426.

It will be interesting to document the effects of increasing doses of 9426 in children. At what point will further increases in dose produce no further shortening in onset time? How will increasing the bolus dose of 9426 prolong recovery? Will the duration of paralysis be simply related to the dose, or will the rate of recovery decrease as the dose increases as has been shown for vecuronium? The answers to these questions will define the clinical utility of 9426 as a facilitator of intubation in pediatric patients. Given the age-related effects of vecuronium and the differences between 9426 and vecuronium that have already been observed in children, it will be interesting to observe the effects of 9426 in infants.

CONCLUSION: A CLINICAL PERSPECTIVE

When a neuromuscular blocking drug is administered to a patient for the purpose of facilitation of intubation, the rapidity of onset of effects and the predictability of the degree of paralysis produced by bolus administration of the drug are the factors that determine the relative usefulness of the drug. Both rapidity of onset and predictability of effect are a factor of dose of the drug administered. When a dose of drug equal to several times the ED_{95} is administered, it is likely that complete paralysis will be produced as rapidly as possible. Thus, if it is useful to compare the effects of equipotent doses of drugs, it is useful to discuss age-related differences in potency. An important reason that the same dose in milligrams per kilogram of neuromuscular blocking drug will have somewhat different effects in patients of different ages is that it is not equipotent in all these patients.

It is clear that the most rapid onset of paralysis can be obtained with succinylcholine. However, in pediatric patients several nondepolarizing neuromuscular blocking drugs can produce paralysis that reliably facilitates intubation within a few minutes. Onset of effect is usually more rapid in younger patients. Because large doses of 9426 can produce complete paralysis in adults in 1 to 2 minutes, it may be that equipotent doses of 9426 will produce complete paralysis of pediatric patients even faster. In many situations in the practice of pediatric anesthesia, a 1- to 2-minute delay in onset of paralysis is acceptable. Then nondepolarizing neuromuscular blocking drugs currently available can be used in lieu of succinylcholine, thus avoiding the side effects of the depolarizing drug.

The duration of action of a bolus of neuromuscular blocking drug can vary significantly with age. Because of the wide interindividual variability in response to neuromuscular blocking drugs, which has been appreciated by those who care for patients for many decades, knowledge about the pharmacokinetics and pharmacodynamics of these drugs cannot replace careful monitoring of each patient. However, knowledge of the expected duration of action of a drug should influence the choice of neuromuscular blocking drug administered. In general, one would expect that a drug with greater potency would have a greater duration of action. However, recent observations of the effects of neuromuscular blocking drugs in pediatric patients demonstrate that this generalization is false. Under some anesthetic conditions, infants may recover at a similar rate or more rapidly than do older children from paralysis induced by pancuronium or pipecuronium. It also appears that infants and children recover more rapidly than do adults from the effects of neuromuscular blocking drugs that are largely metabolized in the plasma, atracurium and mivacurium.

It is difficult to precisely define adequacy of recovery from neuromuscular blocking drugs. Recovery of the train-of-four ratio, of adductor pollicis function, to at least 0.75 has been accepted as a minimum. It has been demonstrated that the evoked function of the diaphragm is resistant to the effects of neuromuscular blocking drugs. The ED_{90} for pancuronium at the diaphragm was 1.6 to 1.7 of the ED_{90} at the adductor pollicis, and there was no significant difference in this ratio with age from less than 1 to 10 years of age.[36] Yet it is an assumption that evoked neuromuscular function of the thumb should be similar to spontaneous neuromuscular function of the airway and other muscles of respiration. Obviously, anesthetic drugs affect spontaneous neuromuscular function. Even when neuromuscular function appears to be adequate, the subjective sensation of weakness may persist. Thus, it would appear appropriate to administer neuromuscular blocking drugs from which the patient, pediatric or adult, may be expected to recover at a rate similar to the expected recovery rate from the drugs that produced anesthesia.

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Postoperative Pain Management for Children

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> We must all die. But that I can save (a person) from days of torture, that is what I feel as my great and ever new privilege. Pain is a more terrible lord of mankind than even death himself.
>
> ALBERT SCHWEITZER

MORPHINE INFUSIONS (MORE CONSISTENT ANALGESIA WITHOUT THE "OWIE")

In the last 10 years there have been major advances in the understanding of the pharmacokinetics and dynamics of morphine when it is administered to children for pain relief. Previously, either no narcotic was recommended for use in providing analgesia for young children, or the dose or route recommended was inadequate to provide consistent pain relief. As a result, the use of narcotics in children was limited to intramuscular or subcutaneous techniques on surgical wards; intravenous (IV) techniques were restricted to use in monitored environments or under the direct supervision of a physician only. There is now adequate evidence to show that continuous morphine infusion can provide good analgesia for children in most environments, because consistent blood levels of analgesic are provided using this technique. The result is improved patient comfort.

In 1979, Dahlstrom et al[22] improved understanding of the pharmacokinetics of morphine when they studied children aged 1 month to 15 years, demonstrating only minor differences in the kinetic patterns of morphine at different ages. Dahlstrom et al failed to show any differences in sensitivity to morphine between children of different ages.

Continuous infusion of morphine has been used for analgesia in the intensive care unit for a number of years, as patients are closely monitored for complications, and the sedative effects of morphine facilitate controlled ventilation. Several recent clinical studies have been done to demonstrate its effectiveness in this setting. In a group of children who had undergone cardiac surgery, Lynn et al[51] from the

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Children's Orthopedic Hospital and Medical Center in Seattle, Washington, demonstrated that continuous infusions of morphine at 10 to 30 μg/kg/h provided satisfactory analgesia and did not interfere with spontaneous ventilation, even though there was a fivefold variation in measured morphine serum levels. Millar et al[64] identified an often erratic and inappropriate prescription and administration of postoperative analgesia to patients in the intensive care unit at the Red Cross War Memorial Children's Hospital in Cape Town, South Africa. Therefore, they initiated continuous morphine infusion to provide pain relief for 20 children aged 3 months to 12 years who had undergone general surgical procedures. Blood levels of morphine were measured and shown to be 4.8 to 9.3 ng/mL, with rates of continuous infusion varying from 24 to 28 μg/kg/h. It was recommended that each patient's analgesic requirements be determined individually, rather than by the fixed dose.

Fortunately, several individuals have adopted the continuous infusion technique used in the intensive care environment and applied it to use in postoperative wards. In 1983 Bray[12] described a technique of continuous infusion of morphine in postoperative patients at the Fleming Hospital for Sick Children in Newcastle-Upon-Tyne, England. A bolus of 200 μg/kg of morphine was administered, followed by a continuous infusion at 20 μg/kg/h. He compared the number of "unacceptable hours" of pain experienced by 20 children receiving either continuous IV morphine infusion or intermittent intramuscular injection of morphine, demonstrating that infusion provided consistently better analgesia. Subsequently, he established that this prescription for continuous infusion in children aged 10 months to 15 years provided measured blood levels of approximately 16 to 18 ng/mL at steady state.[11] In Melbourne, Australia, at the Royal Children's Hospital, continuous infusion of morphine was being used in the intensive care unit for provision of sedation and analgesia, as has been the case in many other pediatric institutions. Motivated by the effectiveness of continuous infusion in providing analgesia in the intensive care environment, Beasley and Tibbals[5] in 1987 explored the possibility of using continuous morphine analgesia for children on a surgical ward; they published a prospective study of 121 subjects assessing the efficacy and safety of infusions for postoperative analgesia. Complications encountered were vomiting (19%) and drowsiness (12%), with no recorded instances of respiratory depression. Although the numbers studied were not sufficient to identify rare complications, the investigators made a useful contribution in providing guidelines for weight (over 5 kg) and dosage (10–40 μg/kg/h), and they listed standard orders for children receiving continuous morphine infusion in a ward environment. The use of continuous infusion of morphine for postoperative infusion has been used by others,[40] its effectiveness has been confirmed for application after a variety of surgial procedures, and it has been advocated for use in all children but neonates.

Limited use of narcotics for neonates persists.[71] Unfortunately, there are few reliable studies of narcotic effects in the very young (< 1 month of age). Studies that have been done indicate that some neonates, particularly in the early days of life, have a reduced clearance of morphine, variable elimination of the drug, and increased sensitivity to toxic effects. As a result, use of any narcotics in the newborn calls for close monitoring and supervision of the patient after administration of the drug. Koren et al[44] studied 12 newborn infants who were given IV morphine for postoperative analgesia, demonstrating that newborn infants have an increased sensitivity to morphine. The subjects studied were 1 to 49 days of age and were of gestational ages from 35 to 41 weeks. Using a loading dose of 50 to 100 μg/kg and a constant infusion of 6.2 to 40 μg/kg/h, the investigators demonstrated there was great variability in measured morphine plasma concentrations, and that concentrations decreased with time in some subjects, suggesting an improvement in morphine clearance. The variability in concentrations and the development of generalized seizures in two infants led the investigators to suggest restrictions in the dosing of morphine infusions for newborn infants: the infused dose is suggested not to exceed 15 μg/kg/h. This variability in the kinetics of morphine in the newborn has been demonstrated by others.[69]

BUPRENORPHINE (A ROLE FOR SUBLINGUAL USE?)

Buprenorphine, a partial opiate-receptor agonist with potent analgesic properties has recently been studied to determine its effectiveness in providing postoperative analgesia. In a monitored release of the drug, complications were few.[38] A double-blind multiple-dose comparison of buprenorphine with morphine for pain following lateral thoracotomy demonstrated that the analgesic properties were similar to those of morphine, but two patients developed ventilatory depression following repeated doses of buprenorphine.[55] Because these investigators believed that "continuous infusion of morphine cannot be considered safe outside the recovery room or intensive care unit," sublingual buprenorphine was compared with intramuscular morphine for postoperative pain relief in 60 children undergoing orthopedic surgery.[56] There was a high incidence of unsatisfactory analgesia in both groups, although analgesia with sublingual buprenorphine was as effective and reliable as with intramuscular morphine.

PATIENT-CONTROLLED ANALGESIA (LET THE PATIENT DECIDE)

There is evidence that patient-controlled analgesia (PCA) can provide analgesia superior to that of predetermined fixed dosing of narcotics. In addition, an overwhelming proportion of patients who have used both intramuscular narcotics and PCA following surgery express a strong preference for the latter.[73] In a recent editorial in the *Canadian Journal of Anaesthesia,* L. Brian Ready emphasizes the benefits of PCA as a major advance in the treatment of postoperative pain with both clinical and economic benefits.

In the early days of PCA, equipment was limited in its applicability to children, but recent improvements in the pump technology and understanding of its limitations make it easier to use in children. In order to use PCA effectively, a child must (1) have an ability to push the button (or squeeze a bulb); (2) understand the relationship between pushing the button and medication delivery; (3) trust that the amount of medication being delivered is in a safe range; and (4) understand that the expected outcome is pain control, not elimination of pain.[72]

PCA, in the last few years has established a role in postoperative analgesia for children as young as 4 years of age, although most centers have, to date, reported restrictions to a lower age limit of 6 years.

PCA has been shown in children to have a limited number of complications.[34, 75] Most of the complications related to PCA are the result of the drug used, rather than the route and schedule of administration. Burning at the site of injection has occurred, principally related to the size of the bolus injection. Caution has been expressed regarding the participation of parents, because allowing a parent to administer PCA to a child eliminates one of the safeguards of PCA, and the child may receive an excessive dose of narcotic. In our experience at the Alberta Children's Hospital, the major impediment to the acceptance of PCA was a lack of consistency in physician's orders and insufficient staff education before its use on the wards, rather than the fear of complications.

PCA now has an established role for use in older children and the adolescent[91, 97] for both short- and long-term[65] use. Recent studies have inconsistent results when the total dose of morphine used is compared with parenteral narcotics administered in a traditional way. Although Gaukroger et al[33] have suggested that scoliosis patients seem to use more morphine than other groups of patients, this conclusion remains to be confirmed.

Each center seems to have established a routine order for continuous infusion, bolus size, and maximum hourly dosages. The prescription ordered depends on the dilution of drug used, the type of pump used, and the desirability of using a continuous infuson mode with the PCA. Regardless of the prescription written, each patient requires follow-up assessment for modification based on usage.

The use of PCA has obvious advantages. The comfort provided is prompt, independent of the availability of a nurse, regulated according to the need judged by each individual patient, and painless. It also offers the advantage of pretreatment for incident pain such as coughing, moving, ambulation, or physiotherapy, enhancing comfort during these activities. In addition, there is some evidence[96] that the use of PCA rather than intramuscular narcotics offers (1) less pain in the recovery room, surgical ward, and at home following discharge from hospital; (2) more rapid recovery of normal minute ventilation, and normal body temperature; (3) reduced need for postoperative antibiotics; (4) earlier return to a solid food diet; and (5) earlier discharge from hospital with subsequent smoother convalescence at home over the following 2 weeks.

Although morphine is usually used for PCA, meperidine is used in some institutions. It must be recognized that complications may be associated with its use, and complications may be different than those experienced with morphine. Meperidine is metabolized by the liver through two primary pathways: hydrolysis by carboxyesterase to meperidinic acid; and N-demethylation by microsomal hydroxylation to normeperidine. Of these metabolites, normeperidine is active and has an elimination half-life of 24 to 48 hours; this product has half the analgesic potency and twice the neurotoxicity of meperidine. As a result, jitteriness, tremors, myoclonus, and convulsions may appear after several days of meperidine use, as toxic manifestations of normeperidine. This effect is enhanced with oral use of meperidine (because of first-pass metabolism), with impaired renal function, and in the presence of medications that enhance microsomal enzyme activity (chlorpromazine, phenobarbital, and phenytoin). When meperidine is used for postoperative analgesia, these recently described complications[36, 47] should be considered.

One of the major advantages of PCA is that analgesic administration is individualized for each patient based on the need identified by the patient, and this is particularly useful for the postsurgical patient, whose needs may change by the hour. Morphine distribution is significantly altered by anesthesia and major surgery.[23] In addition, morphine consumption during PCA may vary fourfold between patients, although hourly consumption based on a mean for all patients has been shown to be equal to the dose that is traditionally recommended for parenteral administration. The use of PCA allows patients to control for these variables by adapting the administered dose to their own needs.

Although analgesia provided by PCA appears to be automatic, it is important that consistent standards for use be applied in each institution, that access to the pumps be regulated to ensure consistency and reliability of the equipment, and that educational activities be provided to update nursing and medical staff as needed. Using a set of standardized orders, continually reevaluating their effectiveness, and modifying the orders according to each patient's need all enhance the effectiveness of PCA.

As one modality of several that are now used for providing postoperative pain control, PCA is used optimally with coordinated medical and nursing supervision.

REGIONAL ANESTHESIA FOR CIRCUMCISION (IT DOES HURT!)

Although regional anesthesia has been used for many years, there has been a resurgence in interest regarding its application to pediatric patients in the last 10 years. Of particular interest has been local and regional blockade of pain for circumcision and postcircumcision pain relief. For centuries, circumcision has been carried out without the benefits of local or systemic analgesics in the belief that either circumcision does not hurt or pain relief is not needed. Recent investigations have demonstrated that circumcision does elicit a pain response[87] in the newborn undergoing circumcision, and that nerve block of the penis[57] will minimize the pain response. In order to minimize postoperative pain, dorsal nerve block of the penis, parenteral narcotics, and epidural narcotics have all been used as alternative forms of management for circumcision in children.[53, 98] Early studies with caudal epidural bupivacaine were conducted using a 0.5% solution, rather than 0.25% bupivacaine, and motor blockade complicated the postoperative pain management.[3, 50, 103] As a result of the motor blockade and fears of other potential risks associated with caudal blockade, dorsal nerve block of the penis,[18, 48, 66, 76] topical application of local anesthetic,[2] and subcutaneous ring block of the penis have all been advocated for relief of postcircumcision pain.

Despite the many laudatory papers advocating the use of nerve block of the penis and its absence of complications, serious complications may occur. Sara and Lowry[79] identified two patients who experienced gangrene of the skin of the penis after having undergone circumcision under general anesthesia combined with dorsal nerve block of the penis. They pointed out that the dorsal arteries of the penis are basically end arteries and recommended that it would be prudent to inject away from the pubic bone, at right angles to the shaft of the penis as it is held outstretched.

Topical analgesia for postcircumcision pain was compared with morphine and with dorsal nerve block in a study published by Tree-Trakarn and Pirayavaraporn.[89] Topical analgesia was found to be highly effective in relief of postoperative pain, using a single application of topical lidocaine on the wound at the termination of surgery. A subsequent study[90] demonstrated that repeated application of lidocaine jelly is convenient and effective for prolonging the duration of postoperative analgesia.

Broadman et al[13] described the use of a subcutaneous ring block of the penis for postcircumcision pain relief. In a study of 50 patients, 25 received a subcutaneous ring block. Of those subjects receiving a ring block, 5 (20%) required IV fentanyl in the recovery room. The investigators advocate subcutaneous ring block as a simple and effective means of providing postcircumcision analgesia.

INTRAPLEURAL BLOCK (IS THIS A VIABLE ALTERNATIVE?)

Motivated by a successful application of intrapleural analgesia in adults after mastectomy, cholecystectomy, and renal surgery, McIlvaine et al[60] assessed the continuous infusion of bupivacaine via intrapleural catheter for analgesia after thoracotomy in children. The intrapleural catheter was placed by the surgeon before closure, and loosely sutured to the posteromedial aspect of the incision. Using a continuous infusion of bupivacaine 0.25% via the pleural catheter at a rate of 0.5 mL/kg/h, narcotics were not required for analgesia in any patient during the infusion. Measured plasma concentrations of bupivacaine were high in the majority of the 14 patients studied: greater than 2 μg/mL in 11 of 14 patients; greater than 4 μg/mL in five patients; and greater than 7 μg/mL in one patient. Unfortunately, maintenance of the block was demonstrated to require that the patient remain supine. In a subsequent publication, McIlvaine et al[61] described 24 patients who had an intrapleural catheter placed either percutaneously or under direct vision, and the technique was described as promising for relief of postoperative pain.

INGUINAL HERNIA AND ORCHIDOPEXY (WHY NOT A REGIONAL BLOCK?)

It is possible to do inguinal surgery under regional blockade alone. Most children require general anesthetics as well, however, and therefore ilioinguinal/iliohypogastric nerve blocks are frequently performed in children principally to enhance postoperative analgesia.

Shandling and Steward[83] from the Hospital for Sick Children in Toronto, Canada in 1980 described the use of an ilioinguinal/iliohypogastric nerve block with 0.5% bupivacaine intraoperatively. They demonstrated a marked reduction in the requirement for analgesics in the recovery room. Of the 156 patients studied, the only complication encountered was the occurrence of a transient motor block of the femoral nerve in three patients. This investigation was helpful in demonstrating the usefulness of regional inguinal block in improving postoperative analgesia. The occurrence of quadriceps paresis was subsequently described in additional patients who had local inguinal block with 0.5% bupivacaine by Roy-Shapira et al.[78]

In 1987, Cross and Barrett[21] compared ilioinguinal/iliohypogastric nerve block with caudal anesthesia for patients undergoing inguinal hernia repair and orchidopexy, using 0.25% bupivacaine with epinephrine. No significant difference was demonstrated betwen the groups in the duration or quality of the analgesia provided by the two techniques; all subjects were premedicated with a narcotic, which confuses the issue of assessment of postoperative pain. A study in the same year by Reid et al[74] compared ilioinguinal/iliohypogastric nerve block with wound infiltration in 49 boys undergoing inguinal hernia repair; no difference was shown betwen the two techniques in quality of postoperative pain relief assessed by mood and parental reporting.

CAUDAL EPIDURAL ANALGESIA (WHY DIDN'T WE THINK OF IT EARLIER?)

Technique and Efficacy

Since the early 1970s the use of caudal epidural blockade with local anesthetic solutions for lower abdominal genitourinary, and orthopedic surgery has become increasingly popular in children[43, 49] and is now in widespread use.[24, 102] This block is more popular in children than in adults for two reasons. First, it is simple to perform because of the ease with which the sacral hiatus can be palpated in most children. Second, cephalad spread of local anesthetic solutions is more reliable and predictable in children than in adults. This is probably due to the fact that in children under 8 years of age the epidural fat is loose and gelatinous, after which time it becomes more fibrous and dense.[81, 82] The age of this anatomical change coincides with the age at which the extent of spread of local anesthetic solutions injected caudally becomes more variable.[25, 58]

Caudal epidural blockade is perceived to provide the patient with intraoperative as well as postoperative benefits. Intraoperatively, it allows general anesthesia to be maintained with reduced doses of anesthetic agents. Postoperatively, it can provide effective analgesia without the use of narcotics. A single bolus of local anesthetic given by this route may provide effective postoperative analgesia for up to 23.5 hours.[95] Catheters may be introduced into the epidural space via the sacral hiatus and may then be used for intermittent or continuous administration of local anesthetic in order to provide prolonged postoperative analgesia. This technique has not, however, gained great popularity because of difficulty with catheter fixation and fears of infection due to proximity to the rectum. It does have a place when the lumbar approach to the epidural space is not feasible. Berde[7] recommends that caudal epidural catheters be used for a maximum of 72 hours.

Dalens and Hasnaoui[25] compared 1.5% lidocaine with 0.25% bupivacaine for caudal blockade in children. The sensory block produced by 0.25% bupivacaine lasted significantly longer than that produced by 1.5% lidocaine. Lidocaine will hasten the onset of caudal epidural blockade and may enhance the intensity of block intraoperatively, but it does not augment postoperative analgesia.

Bupivacaine is the principal local anesthetic used for caudal blockade in children because of its prolonged duration of action. Its reported duration of action in the postoperative period can normally be expected to provide from 4 to 10 hours of postoperative pain relief after various types of surgery.[10, 52, 94, 100] This pain-free period is long enough to ensure that most patients having minor inguinal or genital surgery will not require any narcotic analgesics in the postoperative period.

The number of different dosage schedules that have been proposed for caudal epidural blockade in children would seem to indicate that none are entirely satisfactory.[4, 15, 17, 30, 37, 42, 80-82, 85, 86, 95] Schulte-Steinberg and Rahlfs[82] recommended 0.1 mL per spinal segment per year of age + 0.1 mL per spinal segment as an appropriate volume of local anesthetic for caudal blockade in children. Armitage[4] claimed such volumes were not large enough to be uniformly effective and recommended volumes of 0.5 mL/kg for blockade of sacral nerves, 1.0 mL/kg for blockade of lower thoracic nerves, and 1.25 mL/kg for blockade of midthoracic nerves.

One of few studies to compare the efficacy of different dosage schedules compared that recommended by Armitage to that recommended by Coad and Hain[19] in children undergoing inguinal hernia repair. Coad and Hain recommended use of bupivacaine 0.25% or 0.5% in volumes of (0.1 × age [years] + 0.2) milliliter per segment to be blocked. Adherence to the Coad and Hain dosage schedule led to the use of smaller volumes of bupivacaine with comparable postoperative analgesia for the 5-hour study period, and the authors recommended use of the Coad and Hain dosage schedule on this basis. Unfortunately, the authors did not compare duration of analgesia between the two dosage schedules. Warner et al[95] provided evidence that a caudal block will contract with time so that a higher block (produced by a larger volume of local anesthetic) will provide effective pain relief for a longer period of time. In addition, the subjects in this study were young (mean, 2.5 ± 1.2 years), and local anesthetic tends to spread cephalad in this age group. As a result, the extrapolation of their recommendations for use in an older age group is limited; older children may require comparatively larger volumes of local anesthetic for the same clinical effect.

A number of different workers in this area seem to be approaching consensus regarding the optimum dosage schedule. Dalens and Hasnaoui, in reporting 750 caudal blocks in children using four different volumes of local anesthetic solution reported segmental levels of blockade (Table 1).

Dalens and Hasnaoui noted that the upper limit of analgesia varied widely,

Table 1. *Volumes of Local Anesthesia Solution Required for Segmental Levels*

VOLUME (mL/kg)	MEAN HEIGHT OF BLOCK	RANGE
0.5	T11	L3–T9
0.75	T10	L1–T6
1.0	T8	L1–T2
1.25	T5	T8–T1

especially in children over 7 years of age. They recommended volumes of 0.75 to 1.0 mL/kg of local anesthetic solution for inguinal surgery, as these two volumes gave an appropriate height of block in 82% and 85% of patients, respectively. Similar recommendations have been made by other authors. It is important to note that 1.25 mL/kg of solution resulted in an excessively high segmental block (>T4) in 29% of patients. This report confirmed the variable effect of similar volumes of local anesthetic in different patients.

In the past, 0.25% bupivacaine has been recommended as the optimal effective concentration for caudal blockade in children.[14, 42] In 1988 Wolf et al[100] evaluated three concentrations of bupivacaine with epinephrine and concluded that bupivacaine 0.125% is associated with significantly less motor blockade than bupivacaine 0.25%, while providing similar postoperative analgesia. Therefore, they stated that bupivacaine 0.125% is preferable to the higher concentration.

Epinephrine should be added to bupivacaine in order to prolong postoperative analgesia. Warner et al[95] studied 341 children undergoing inguinal or genital surgery and evaluated the effects of epinephrine on the duration of analgesia using 0.25% bupivacaine. Epinephrine 1:200,000 prolongs the duration of analgesia, most markedly in children under 6 years of age. After inguinal surgery in children under 6 years of age, duration of analgesia was a mean of 18 hours when epinephrine was added compared with 8.1 hours with plain bupivacaine. In children 6 years of age and older duration of analgesia was 9.1 hours compared with 6.5 hours for the plain solution. On the basis of these results, the investigators recommended epinephrine 1:200,000 be added to bupivacaine in order to prolong analgesia, especially in young children.

There is a clinical impression among many anesthetists that a caudal block after inguinal or genital surgery will provide superior pain relief to systemic narcotics. This was not confirmed by Bramwell et al,[10] who demonstrated that postoperative analgesia using caudal block is superior after circumcision, but not after herniotomy or orchidopexy, for which caudal anesthesia is comparable but not superior to systemic narcotics. The authors suggested that this was because circumcision is more painful than herniotomy or orchidopexy. An alternative explanation may be that the analgesic dermatome level in some subjects was not high enough to cover the painful dermatomes after herniotomy or orchidopexy. Since the study did not test dermatomal level of analgesia, we cannot be sure that all blocks were adequate. A subsequent study by Dalens et al[25] demonstrated a small but significant failure rate of caudal blockade, which is usually due to inadequate height of blockade. Inadequate height of blockade may therefore explain the inconsistencies between clinical impressions and the findings in this study.

A number of recent studies have shown that after inguinal surgery, caudal blockade provides comparable analgesia to both wound infiltration with local anesthetic and ilioinguinal block.[32]

Adverse Effects

Instructions regarding the technique of caudal block usually recommend the use of a short needle but in recent years some practitioners have recommended use of a plastic IV cannula for this purpose.[9] It is believed that use of a cannula rather than a needle enhances cephalad spread of local anesthetic and reduces likelihood of dural or vessel puncture, although these assertions have not been studied. Use of short and long beveled needles has been studied, however. Dalens et al[25] demonstrated that short beveled needles are less likely to puncture epidural vessels than long beveled needles.

Caudal blockade has a low incidence of serious adverse effects in children. Potentially serious complications are subarachnoid injection of local anesthetic, which may cause a "total spinal," intravascular or intraosseous injection of local anesthetic, which may cause systemic toxicity, and needle trauma to nerves and other tissues. Total spinal anesthesia has been reported after attempted caudal blockade,[28] as has systemic toxicity[54] and penetration of pelvic viscera.[27] However, these complications are rare.

Adverse effects that may occur after correct placement of local anesthetic include nausea and vomiting, leg weakness due to motor blockade, urinary retention due to decreased bladder sensation, hypotension due to sympathetic blockade, and apnea due to excessive spread of local anesthetic within the epidural space.

The reported incidence of nausea and vomiting is 5% to 30% and does not seem to be less in patients who have received narcotics.[24, 25] As nearly all of these patients have received a general anesthetic as well as a caudal block it is often difficult to apportion blame for this complication.

Leg weakness from residual motor blockade is directly related to the concentration of local anesthetic used and may delay discharge of day patients. Yeoman et al[103] found that 31% of patients were unable to walk 6 hours after caudal bupivacaine 0.5%. Vater and Wandless[94] found that 8% of patients were unable to stand 6 hours after caudal buivacaine 0.25%, and Wolf et al[100] found that 85% of patients could stand as early as 1 hour after bupivacaine 0.125%. Clearly, lower concentrations of bupivacaine are advantageous in this regard.

A number of investigators have stated that urinary retention due to decreased bladder sensation is common up to 10 hours into the postoperative period, but this is rarely a serious problem and does not delay discharge of day patients.

Significant hypotension due to sympathetic blockade is very rare after caudal block in children under 5 years of age and in older children, in the absence of hypovolemia.

Dalens et al[25] reported excessive spread of local anesthetic within the epidural space after caudal blockade causing apnea without cardiovascular instability. In the two cases reported the period of apnea was brief and without sequelae.

Caudal Block Using Narcotics

In 1979 the first reports of epidural narcotic administration in humans were published.[6, 20] Since then, epidural narcotics have been used extensively in adults. From this experience there is consensus that epidural narcotics can provide prolonged postoperative analgesia, particularly if hydrophilic drugs such as morphine are used. In addition, morphine doses do not need to be administered near the dermatomal segment of pain, probably because of spread within the cerebrospinal fluid. Thus, morphine administered into the caudal space can provide thoracic analgesia after surgery. Nausea and vomiting, urinary retention, and pruritus are common, and delayed respiratory depression is rare but potentially dangerous.

Epidural narcotics have been used in children, and the limited experience to date shows that they have the same advantages and limitations in children as they do in adults. Although caudal morphine has been used in children after orthopedic, genitourinary, abdominal, and thoracic surgery,[77, 93] the number of patients studied is small, and only a limited number of conclusions are possible.

Several recent studies have reviewed the use of caudal morphine for both inguinal and genital surgery.[41, 45, 99] They have recommended that 50 to 100 μg/kg of caudal morphine can be expected to provide prolonged analgesia (8–24 hours) without an increase in side effects when compared with caudal bupivacaine. Because of small numbers of subjects, estimation of the incidence of side effects is unreliable, especially with regard to an uncommon complication such as respiratory depression.

Decreasing the dose of epidural morphine has little effect on the duration of analgesia and may decrease the incidence of side effects. Krane et al[46] have compared 33, 67, and 100 μg/kg of caudal morphine after major abdominal, genitourinary, or orthopedic surgery and have found the duration of analgesia to be 10.0, 10.4, and

13.3 hours, respectively, with a similar incidence of side effects in the three groups. One child in the 100 μg/kg group developed delayed respiratory depression. On the basis of this study the authors recommend 33 μg/kg of caudal morphine as an initial dose in children.

Nausea and vomiting after caudal morphine are common side effects, occurring in approximately 40% of patients. Pruritus is also common but is rarely severe enough to require treatment. The incidence of urinary retention is variable; in some studies it has been no more common than in children receiving caudal bupivacaine or systemic narcotics. Valley and Bailey[93] found that the incidence of urinary retention was high; they stated that 10 of 56 children required catheterization for urinary retention after 70 μg/kg of caudal morphine was administered after various types of surgery.

Respiratory Depression: Is It a Problem?

Delayed respiratory depression after caudal morphine does occur in children as it does in adults. Valley and Bailey have reported 11 cases of respiratory depression in 138 administrations of caudal morphine. All were within 12 hours (mean, 3.8 hours) of morphine administration, and 10 were in children 12 months of age or younger. This represents an 8% incidence of respiratory depression, which is much more frequent than in adults. However, this was a retrospective uncontrolled study in which 60% of subjects received concomitant IV narcotics intraoperatively, 54% of subjects were under 12 months of age, and in which the surgery was major. We do not know the number of former premature infants involved in the study. It may be that some of these subjects would have developed respiratory depression even if caudal morphine had not been used. The use of IV as well as epidural narcotics is recognized as a factor contributing to the increased risk of respiratory depression in these subjects. Accurate estimation of the incidence of respiratory depression in children after caudal narcotics requires further study.

In view of the risk of respiratory depression, how should children be monitored after receiving epidural narcotics? This question has not been resolved, but a common practice has been to provide 12 to 24 hours of continuous cardiorespiratory monitoring subsequent to the last dose of epidural narcotic. It may be that excessive sedation is an earlier sign of respiratory depression after epidural narcotics than bradycardia or decreased respiratory rate, and it has been suggested that "the best monitor for respiratory depression is an alert nurse looking for unusual somnolence."[92] Naloxone and resuscitation equipment should be immediately available, as should a physician capable of airway management.

LUMBAR AND THORACIC EPIDURAL ANALGESIA (FINALLY, COMPLETE PAIN RELIEF)

Intramuscular or IV narcotics provide effective pain relief, but their administration does not eliminate pain; the use of epidural analgesia can provide this. Continuous epidural analgesia has been used in obstetrics for a number of years to alleviate the pain of labor and delivery, and its use has recently been extended to the treatment of both acute and chronic pain. As a result of increased interest in regional anesthesia techniques for intraoperative and postoperative analgesia, there has been an evolution toward the use of caudal, lumbar, and thoracic epidural analgesia for children requiring both intraoperative and postoperative pain control. The introduction of bupivacaine, which will provide analgesia without motor blockade, and the recent development of small, high-quality epidural needles and catheters have been particularly helpful in improving total pain relief.

In the last 7 years, a number of innovative anesthetists have been instrumental in advancing the use of lumbar epidural analgesia for intraoperative and postoperative use in children. Meignier et al[62] described six children with respiratory disabilities, weighing 4 to 15 kg, who had undergone abdominal surgery, followed by placement of an epidural catheter for postoperative continuous epidural analgesia. The catheter was left in place for 48 to 72 hours, and the patients received bupivacaine 0.25% without adrenalin at 4 mg/kg/d. This form of postoperative analgesia was successful for this group of children, all of whom had respiratory disabilities—it was thought that adequate postoperative pain relief improved postoperative pulmonary function. Shapiro et al[84] described the use of thoracic epidural morphine via an epidural catheter for five children who had undergone thoracotomy and were being managed in the intensive care unit; analgesia lasted 8 to 25 hours following each initial dose of morphine. Glenski et al[35] used a lumbar epidural catheter for 15 major surgical procedures in children, most of whom were adolescents, and the quality of pain relief was desribed as excellent. Morphine was used in a dose of 0.07 to 0.11 mg/kg, and the mean duration of analgesia from each bolus was 6.3 to 18 hours. Complications of the epidural morphine were similar to those experienced in adults: pruritis, nausea, and urinary retention. These uses of epidural catheters stimulated interest in using epidural analgesia for other applications.

Dalens et al[26] explored the feasibility of using epidural anesthesia to supplement general anesthesia and to facilitate postoperative analgesia. They used a single-shot epidural anesthetic with a mixture of local anesthetic solutions and morphine in children from 2 days to 7 years of age. Significant side effects related to the administration of morphine occurred: itching, nausea and vomiting, and urinary retention. Although there was an unacceptably high number of subarachnoid punctures using the Potts-Cournand needle, the effectiveness of epidural morphine for postoperative analgesia in children was established, subject to technical improvements.

Ecoffey et al[31] demonstrated in 1986 that both lumbar and thoraic epidural analgesia are feasible alternatives for providing postoperative pain relief in children from 3 to 36 months of age. These investigators established the cardiovascular effects of epidural injection of 0.25% bupivacaine, the time course and blood levels of bupivacaine after epidural injection, and the extent of epidural spread of injected solution using radiographic examination. They clearly demonstrated that epidural catheter insertion is feasible and of limited risk in children from 1 to 36 months of age and that reliable postoperative analgesia may be provided in this age group via the epidural route. This was a major advance in postoperative pain management for young children, as postoperative pain had previously been managed poorly in this group.

Desparmet et al[29] evaluated the efficacy of continuous epidural infusion with low doses of bupivacaine for postoperative pain relief in children aged 11 months to 15 years. Using a 21- or 20-gauge epidural catheter and a continuous infusion of 0.25% bupivacaine in the postoperative period, bupivacaine plasma levels were measured in the postoperative period, and levels of analgesia were assessed. The reliability of continuous epidural infusion and the low level of plasma bupivacaine concentrations initiated interest in the use of this modality in children for postoperative pain control after major surgery.

In 1987, Murat et al[67] reported their experience with continuous extradural anesthesia in 229 children over a 15-month period. For 155 of the children the epidural catheter remained in place for use in the postoperative period, during which bolus doses of 0.25% bupivacaine were administered. It is of interest to note that the presence of epinephrine prolonged the duration of analgesia with 0.25% bupivacaine (92 compared with 71 minutes). In this study, initiation of the epidural in children younger than 8 years had no significant hemodynamic consequence, but a fall in heart rate and systolic arterial pressure was demonstrated in children older than 8 years. One dural puncture and one intravascular injection occurred. Tachyphylaxis and hypotension were not observed. This report of a large number of children treated with epidural analgesia for postoperative pain was of great interest to the pediatric anesthesia community because of the potential for providing effective and reliable pain relief to young children. Dr. Murat stated:

> . . . before beginning to use extradural anaesthesia, the authors had used analgesics sparingly in the postoperative period; in children younger than 8 yr, opioids were never prescribed. Before this technique was used, postoperative pain was often underestimated and neglected, as a result of the lack of interest of both doctors and nurses. The medical staff is now more sensitive to the patients' comfort and will provide them with analgesics or extradural injections when requested. However, in the youngest children, pain is very difficult to evaluate and top-ups are performed according to requests of parents or nurses.[67]

Anesthetists treating acute pain are now more frequently asked to participate in the management of preoperative pain problems, and advances in the use of continuous epidural infusion have enhanced our ability to anticipate and eliminate phantom limb pain. Patients should be treated with a preoperative epidural if limb amputation is anticipated and preoperative pain is experienced. Preoperative limb pain may predispose patients to phantom limb pain,[63] should amputation of a limb be required. Although limb amputation in children is infrequent, it may be necessary for tumors. Noreng et al[68] have studied adults with preoperative limb pain, placed epidurals in subjects for at least 72 hours preoperatively, and demonstrated that there is no painful phantom limb pain at 1-year follow-up in those who had preoperative epidurals. A preoperative continuous epidural should be considered worthwhile in this group of patients.

NURSES (HOW DID THEY COPE?)

The last decade has seen a dramatic increase in the interest of all health care professionals toward improving the management of postoperative pain. Most physicians and nurses would agree that in the past, pain management in infants and children has been inadequate. Analgesics were given infrequently, sporadically, and in nontherapeutic doses. In working toward the mutual goal of improved pain relief, the two professional groups have taken on varying tasks. The medical profession continues to evaluate an expanding armamentarium of drugs, to improve the understanding of the pharmacokinetics of analgesics in children and to develop alternative administration techniques. Nursing professionals have concentrated their efforts on (1) improving the understanding of how young children communicate pain; (2) developing tools to assist in the assessment of pain, and (3) determining the attitudes and factors that affect a nurse's decision to intervene and to treat pain.

One of the most difficult tasks a nurse faces is the interpretation of what a preverbal child is communicating about pain. Young children cannot effectively communicate the degree or location of their pain. Even when a child can verbalize discomfort, complaints frequently are not acknowledged with the same degree of credibility as might be given to an adult.[59] It is far easier to attribute the pain behavior to separation, fear, anxiety, anger, or sadness[1] especially when the child will settle for varying amounts of time. The fact that a child settles when consoled does not necessarily indicate that pain is not being experienced. Distraction is a powerful tool that children use to temporarily alleviate pain.[39]

Children use both verbal and nonverbal communication to identify their psychophysiologic state. Therefore, it is imperative that important nonverbal clues, in the postoperative period, be acknowledged as evidence of pain.

Sometimes lack of movement, rather than agitation, is a sign of pain. Taylor[88] observed 20 nonverbal children between the ages of 18 months and 4 years who had undergone inguinal herniorrhaphy. During the first 3 hours following surgery the number of movements and vocalizations indicating pain decreased, suggesting that the children reduced their activity as they realized that thrashing, uncontrolled movements increased their pain. The type of movements in which the children engaged also appeared to change in character as guarding of the operative site increased. There was a trend toward immobilization. The quality of the children's vocalizations had distinct characteristics. The first hour consisted of an intermingling of sobbing, wailing, and screaming, in the second hour the incidence of crying decreased, only to pick up again in the third hour. As had occurred with the movements, the nature of the crying changed over the 3-hour period, with screaming eventually becoming the predominant form of crying. The frequency of verbalizations remained stable over the 3-hour period, with the childrens' choices of words, phrases, and statements giving direct evidence that they were experiencing pain. Children in this study were communicating pain through sounds and crying; the extent of movement (thrashing) they demonstrated was not a reliable indicator of the degree of their pain.

The development of a consistent, reliable, and objective tool for pain assessment in children has proved to be a difficult task. Pain is a subjective, individualized experience. What causes discomfort in one child seems to hardly affect another. The variation in responses to similar pain stimuli and the different interpretations and manifestations of pain by children has led to the development of many different types of pain scales. Investigations to date identify two categories of pain scales: those that rate behavioral observations and those that rely on self-reporting.

One of the advantages of the behavioral measures is that they enhance assessment of pain experience in children who are either unable or unwilling to cooperate. Several scales that have been developed include ratings for vocal and facial behaviors as well as trunk and limb actions (Craig, Hester, Elliot, Attia, and Broadman).

The self-reporting scales are divided into those that require little verbal ability on the part of the child (Oucher, Faces, Glasses, Chips, and Colour) to those that require a developed descriptive language (Simple Descriptive Scale, Numeric Scale). Wong and Baker[101] attempted to rate the validity, reliability, and preference of a number of different self-reporting scales. They found that children aged 3 to 18 years preferred the faces scale over the other scales but that no scale was superior in validity or reliability.

Unfortunately, several writers and researchers have noted a disparity between observed behaviors and self-reports. Beyer et al[8] evaluated 25 children aged 3 to 7 years, who had undergone major orthopedic, urologic, or general surgery by examining the patterns of self-reported and behavioral pain scores. Their results indicated a poor correlation between the behavioral measures of pain and two self-reports. The two self-reports, although very different from each other, were strongly, positively, and significantly correlated with each other. The investigators stated the behavior tool used—Children's Hospital of Eastern Ontario Pain Scale—which is a tool based on gross behavioral responses, was not sensitive enough to evaluate preschoolers accurately.

Are nurses prejudiced against children, by downplaying the need of children for analgesia? McGrath et al[59] undertook a study to determine the different perception by nurses of pain experienced by either children aged 9 to 12 years or adults aged 30 to 45 years. The subject's manifestations of pain were presented in vignettes and each nurse's perception of the degree of pain was assessed by requesting (1) a judgement of what action the person in pain should take and (2) a rating of the severity of the pain experienced. It was demonstrated that the nurse observers rated a child's pain in a similar situation as equal to the adult's pain. It was also demonstrated that the suggested interventions for analgesia were similar for both the children and adults. On the basis of these findings, it was suggested that there is no underlying prejudice that would affect a nurse's perception of pain in children.

Why do nurses not intervene when they know additional pain relief may be required? There appear to be at least two reasons. Burokas[16] designed a questionnaire to elicit nurses' goals of postoperative pain relief and their degree of comfort in administering analgesic medication. One hundred thirty-four nurses responded. The results suggested that the unit on which the nurses worked had an influence on the strength of an analgesic preferred. Nurses from both the surgical units and the pediatric intensive care units chose a higher dose of narcotic more often than the nurse in the intensive care nursery. The type of unit also appeared to influence the nurses' comfort with medications. Data suggested that the nurses from the pediatric intensive care unit and the intensive care nursery felt more comfortable with the IV administration of analgesics, whereas nurses from the surgical units preferred the intramuscular route. The second, more significant, influencing factor appears to have to do with what the nurse believes the goal for pain management should be. Only 12% of the nurses participating in this study considered complete pain relief as their goal. The nurses who had incorporated pain relief as a priority for their patients intervened more often with an analgesic and choose a medication of higher strength. Nurses' comfort in administering higher doses of analgesics obviously depends very much on previous clinical experience with high-dose narcotic administration; regardless of previous experience, nurses have not, in the past, attempted to provide complete relief of pain.

Why are analgesics not given as frequently as they could be? Powers[70] conducted a study to identify a correlation between children's rating of their postoperative pain and the nurses' rating of the children's pain. Fifty children aged 6 to 16 years were asked to identify the degree of their pain using a 100-mm visual analogue pain rating scale. Nurses were asked to use the same pain scale and to answer a questionnaire. The questionnaire asked the nurse to identify those factors used to identify the experiences of pain and those factors that influenced their decision to administer medication as needed. The results of a correlation of the visual analogue scores indicated that the nurses were able to assess the child's pain accurately. Responses to the questionnaire indicated that the nurses used both behavioral cues (child's facial expression, holding or guarding the operative site, and not moving easily) as well as verbal cues (crying, whining, and groaning) to identify the experience of pain. The results of this particular study are encouraging because it indicates that the nurses were able to assess a child's postoperative pain accurately. What is surprising is that all of the children continued to report pain during the study despite identification of a need for further analgesia. The time from the last dose of analgesic medication was the factor most often cited as affecting the decision to medicate for pain or not.

It may be concluded that, when an order is written for intermittent, intramuscular, as-needed narcotic, that nurses have administered the amount of medication according to their previous experience, with an objective of providing some, but not complete pain relief. The fact that nurses may recognize that a patient has pain is not as important as the time from the last dose of analgesic medication. If improvement of analgesia is an objective, nurses must be provided with the tools to treat pain adequately using as a focus relief of the patient's pain, not the time and dose of the last analgesic given.

ACUTE PAIN SERVICES (OUR PATIENTS ARE DIFFERENT PEOPLE NOW)

In recent years, advances in the treatment of postoperative pain have resulted in dramatic improvements in patient comfort. Tools are now available to provide all degrees of postoperative analgesia, based on patient need, site of surgery, and (occasionally) equipment and monitoring requirements. Children need no longer fluctuate between unconsciousness and uncontrollable pain, awaiting expiration of the "routine" 4-hour interval. Young children can be treated with continuous narcotic infusions or continuous epidural infusions, eliminating the need for a painful injection every 4 hours. Older children may be treated with continuous narcotic infusions, PCA, and continuous narcotic infusions. Regional anesthesia has reduced the need for any postoperative narcotics after some surgical procedures, and is being used preoperatively for pain relief for some painful conditions.

Nurses need no longer focus on the last time and dose of analgesia, but on the patient's perception of pain. With PCA the patient determines the frequency and amount of drug. With controlled narcotic infusions, the dose of medication may be painlessly increased, and the nurse need not worry about the pain caused (with a needle) in order to relieve pain. With epidural analgesia, patient discomfort is an indication to request adjustment in the rate and concentration of analgesic; in some centers, the nurse may be certified to administer the next dose of narcotic, which will give a prolonged period of pain relief. The use of a bolus technique as the principal modality for epidural analgesia is increasingly being relegated to the "bad old days" because of the inconsistency of pain relief and the need for immediate and urgent medical attention for administration of the epidural medication. Nurses are able to help more, and patients are less unhappy.

An acute pain service requires medical support, a pain service coordinator, collaboration with pharmacy, professional staff committed to the relief of pain, and equipment for delivery of medication and patient monitoring. The supervision of continuous epidural analgesia requires the ongoing assessment and revision of prescriptions by an anesthetist. Anesthesia staff are now required to participate in the education of nurses and other professionals regarding the indications for, management techniques, and complications of the various modalities that are now used for acute pain control. A collaborator (usually a nurse) is required to assist with patient management, establishment of nursing policy, nurse education, and administrative support. Pharmacists must establish procedures for ensuring ready availability of epidural medication, and equipment is required to provide continuous epidural infusion.

Postoperative pain management services for children are in the early stages of development. Continuous IV infusion of narcotics, PCA, and continuous epidural infusion of local anesthetics and narcotics are all used to provide consistent analgesia for many different applications.

Presentations of research at international meetings now frequently involve issues related to postoperative pain management. There is a need to resolve many issues related to the provision of continuous epidural analgesia, such as

1. What is the minimal standard of monitoring?
2. Which techniques will minimize risk and maximize analgesia?
3. Which site (level) of epidural infusion will provide the optimal analgesia for specific procedures, and which drug should be used?
4. What is the optimal duration of infusion to meet specific pain requirements?
5. Which precautions must be taken to minimize the "masking" of surgical complications?

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Oximetry and Capnography Monitoring

*J. Michael Badgwell, MD**

Recent developments in monitoring of oxygenation and alveolar ventilation have dramatically improved the anesthetic care of infants and children. Whereas pulse oximetry gained almost immediate acceptance and widespread use in pediatric anesthesia, capnography in young patients was at first viewed skeptically because of limitations in obtaining accurate measurements.[33] In a review of capnometers in 1986, the editors of *Health Devices* (a medical "consumer's guide" produced by the Emergency Care Research Institute) did not rate the performance of the monitors in neonates and infants because it was "unclear whether a valid end-tidal carbon dioxide (CO_2) measurement could be obtained in these patients."[18] The present article reviews the technology and clinical applications of pulse oximetry and capnography, as well as their effectiveness and limitations in the pediatric age group. I explore how pediatric capnography has become increasingly accurate and how the two monitors, oximetry and capnography, work together to monitor oxygenation and ventilation of infants and children.

PULSE OXIMETRY

Pulse oximetry (SpO_2) and capnometry have become essential monitors in pediatric anesthesiology. Whereas capnometry is "encouraged" for all cases, pulse oximetry is a standard of care.[1] Appropriate use of pulse oximetry requires an understanding of its function, limitations, factors affecting accuracy, and clinical applications.

How Pulse Oximetry Works

Pulse oximetry provides instantaneous measurements of arterial oxygen saturation by determining the absorbance of two specific wavelengths of light by blood as it flows between a light source and a photodetector. Two wavelengths are emitted by the light source: red light at 660 nm and infrared light at 990 nm. During each cardiac cycle, light absorption varies cyclically. Pulsatile absorption (AC absorption) occurs during systole when arterialized blood pulsates into the tissue bed. Baseline absorption (DC absorption) is determined in the tissue bed during diastole. The

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pulse oximeter determines the arterial hemoglobin oxygen saturation (SaO_2) as an absorption ratio of red to infrared wavelengths during the AC and DC components of the arterial pulse.

Physiologic Factors That Affect Pulse Oximetry

Because pulsatile blood flow is a requisite for accurate pulse oximetry, a measurement of SpO_2 may be absent or erroneous in the presence of inadequate pulsatile flow. Pulse oximetry may fail when cardiac output decreases. In this sense, pulse oximetry may be used as a plethysmograph. Likewise, SpO_2 may fail in the presence of marked vasoconstriction. The response to acute changes in SaO_2 may vary according to the site of the SpO_2 sensor. The response time for changes in SpO_2 is 5 to 10 seconds using ear probes and may be up to 30 seconds using finger probes.[39]

Factors That May Interfere with Accuracy

Intrinsic. Methemoglobin has the same absorption coefficient at both red and infrared wavelengths.[13] This 1:1 absorption ratio leads to a saturation reading of 85%. Therefore, in the presence of high levels of methemoglobin, SpO_2 is erroneously low when SaO_2 is greater than 85% and erroneously high when SaO_2 is less than 85%. Carboxyhemoglobin has the same absorption coefficient as oxyhemoglobin at 660 nm.[7] Therefore, if a patient has a 90% oxyhemoglobin and 7% carboxyhemoglobin, the SpO_2 will read 97%. The intravenous administration of some dyes (e.g., methylene blue) produce erroneous SpO_2 readings because the dyes change the absorption characteristics of the blood.[35] Fetal hemoglobin[27] and bilirubin[45] do not affect the accuracy of SpO_2.

Extrinsic. Ambient light interferes with the accuracy of SpO_2 and may be minimized by covering the sensor with an opaque shield. During low perfusion, the pulse oximeter will amplify a small pulsatile absorbance signal. Unfortunately, when a weak signal is amplified, the background noise (static) is also amplified, and the pulse oximeter may generate an erroneous SpO_2 reading. Most pulse oximeters are designed to minimize this problem or to display a plethysmographic waveform for identification of noise. As with all plethysmography, the pulse oximeter will detect a complete loss of peripheral pulse, but is not designed to quantify peripheral blood flow. Pulse oximetry may be used, however, to confirm collateral blood flow to the hand in corroboration with the Allen's test. Many pulse oximeters have a time-averaging mode to help prevent patient motion artifact. These artifact-rejection schemes, however, may also affect the accuracy and response time of the pulse oximeter.

Accuracy During Arterial Hemoglobin Oxygen Desaturation

Most pulse oximeters are accurate to within ±2% (SD) between an SaO_2 of 70% to 100%. In many pulse oximeters, however, the accuracy decreases as the SaO_2 falls below 70%.[40] This may be a moot point in most children, since investigation of the desaturation should begin when SpO_2 falls below about 95%. In children with cyanotic congenital heart disease, however, the accuracy of measurements at low saturations is of great importance.

Clinical Uses

Current standards dictate that SpO_2 be used in every instance of general anesthesia and conscious sedation.[1] This recommendation is based on studies such as the one by Coté et al[12] who found that the incidence of major desaturation events ($SaO_2 \leq 85\%$) decreased when SpO_2 was "available." Although SpO_2 is required in all cases, there are some pediatric cases where SpO_2 is particularly helpful: titration of FIO_2 in infants at risk for retinopathy of prematurity (most authors recommend

SpO_2 = 85%–95%), pulmonary artery banding procedures (desaturation may indicate that the pulmonary artery band is overly restrictive), and cases in which return to fetal circulation may occur (e.g., reopening of the ductus arteriosus). In the latter case, preductal and postductal sensors may be helpful in determining shunt direction. Furthermore, recent evidence indicates that arterial hemoglobin oxygen desaturation may occur during transfer from the operating room to the postanesthesia care unit[28] or while in the postanesthesia care unit despite a wakeful clinical appearance.[42]

Complications

As with any device that contacts patients directly, injury can occur when a pulse oximeter probe is applied. However, few complications have been reported despite its almost universal use. Reported complications include overheating of a damaged light-emitting diodes probe, which resulted in skin blistering in three adults.[41] Additional injuries in adults include digital ischemia that resulted from mechanical pressure by a probe on a finger. One such episode occurred in an elderly woman following prolonged application of a spring-tipped probe in the intensive care unit[8] and one occurred in a 16-year-old patient during anesthesia with controlled hypotension for an 11-hour maxillofacial reconstruction.[11] Complications have also been reported in infants. These include a blister from a probe that overheated, an area of mild skin erosion after an ear probe was applied for over 48 hours, and a localized tanned area caused by the continuous application of a fiberoptic finger probe for 5 days.[23] A third-degree skin burn has also been reported during an magnetic resonance imaging scan. This may have been caused by an electromagnetic field induced in the cable that lead from the pulse oximeter to the finger probe.[37]

These reports remind us of the precautions necessary when using pulse oximetry. All instruments need routine inspection and maintenance. Probes with damaged light-emitting diode components should be discarded. The probe should be positioned such that no pressure or torque is applied to the probe or the finger. After application of the probe, the extremity should be inspected for reduced blood flow. The quality of pulsations should also be monitored and the probe repositioned periodically to prevent prolonged local contact. During magnetic resonance imaging procedures, all cables that are in contact with the patient should be positioned in such a way that conductive loops are not formed.

CAPNOGRAPHY AND CAPNOMETRY

Capnometry is the measurement and numerical display of expired CO_2, whereas capnography is the measurement and graphic display of expired CO_2. If the graphic display is calibrated, capnography includes capnometry. Therefore, capnography is often used to indicate both capnometry and capnography. The use of capnometry without capnography may be considered by some clinicians as illogical, since the latter may be the only guide to the adequacy of gas sampling.[33] In fact, Swedlow[43] has referred to the use of capnometry without capnography as "flying blind."

Gas for analysis of CO_2 may be aspirated from the airway ("sidestream" or more appropriately termed "aspirating" capnography) or analyzed as it flows through a sensor inserted into the breathing circuit ("mainstream" or more appropriately termed "flow-through" capnography). Gas can be measured from any location in the breathing circuit or tracheal tube. If measured from the elbow of the breathing circuit, it is referred to as "proximal" end-tidal CO_2. Measurement from a distal location in the tracheal tube is referred to as "distal" end-tidal CO_2.

The CO_2 may be measured by infrared analysis, mass spectrometry, acoustic spectroscopy,[25] or Raman scattering.[44] In addition, if a capnometer is unavailable, end-tidal gas may be aspirated from the endotracheal tube using a needle and syringe during expiration while the fresh gas flow is disconnected and analyzed for CO_2 in a blood gas analyzer.[9] However, I do not recommend that capnography be measured continuously using a fine needle inserted through the wall of the endotracheal tube because the needle could break and the fragment aspirated into the airway.

Accurate Aspirating Capnography

In capnography, the term accuracy refers to the difference between the measured end-tidal CO_2 ($PETco_2$) values and the true end-tidal values. Although a small physiologic difference may exist between $PETco_2$ and arterial Pco_2 ($Paco_2$) due to the effect of dead space ventilation, $PETco_2$ usually approximates $Paco_2$ in intubated children in the absence of significant lung disease or congenital cyanotic heart disease.[10] In the past, accurate capnography was difficult in small infants ventilated through partial rebreathing circuits because the ratio of tidal volume to fresh gas flow was very small. As a result, the exhaled gas was diluted and the end-tidal gas measurement became an underestimate of the true value. Recent advances, however, have provided several methods of obtaining accurate capnography in small infants.

Accurate aspirating capnography may be obtained with infrared analysis or mass spectrometry using proximal sampling in (1) infants and children weighing more than 12 kg ventilated with a volume ventilator (e.g., an Air-Shields Ventimeter; Healthdyne Co, Hartford, PA) and a Mapleson D partial rebreathing circuit[5] and (2) infants and children of all weights ventilated with a pediatric circle breathing system (unpublished data), a Seimens-Elema Servo Ventilator (Seimens-Elema, Schaumberg, IL),[4] or a Sechrist Infant Ventilator (Sechrist Industries, Inc, Anaheim, CA) and a Mapleson D circuit.[19] In infants and children weighing less than or equal to 12 kg who are ventilated with an volume ventilator and a Mapleson D circuit, respiratory gas must be aspirated from the tracheal tube to obtain accurate end-tidal CO_2 measurements (Fig. 1). The catheter may be positioned at any one of several sites within the tube including the distal end (Fig. 2)[4] or from the midlength of the tube (Fig. 3).[3] The distance between the tip of the sampling catheter and the tip of the endotracheal tube must be less than or equal to 12.5 cm for accurate measurement.[30] Other distal sampling techniques include tracheal tubes with a sampling catheter within the wall of the tube. Although these devices may provide accurate measurements, if the sampling catheter becomes obstructed (such as with

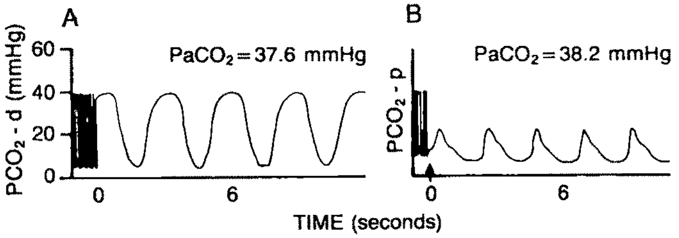

Figure 1. Capnographic waveforms obtained from the (*A*) distal and (*B*) proximal ends of the endotracheal tube in a 6.9-kg 9-month-old infant. The changeover from distal to proximal sampling is indicated by the arrow. Fresh gas flow = 1.8 L/min; respiratory rate = 34 breaths per minute; and peak airway/end-expiratory pressure = 24 cm H_2O. (*From* Badgwell JM, McLeod ME, Lerman J, et al: End-tidal Pco_2 measurements sampled at the distal and proximal ends of the endotracheal tube in infants and children. Anesth Analg 66:959–964, 1987, with permission from the International Anesthesia Research Society.

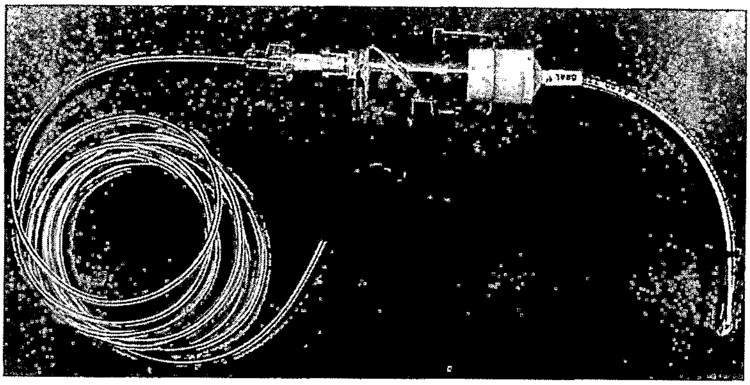

Figure 2. End-tidal Pco_2 may be sampled from the distal end of the endotracheal tube using a 19-gauge Intracath catheter (The Deseret Co, Sandy, UT) inserted into a clear plastic elbow with a central Leur-lok connection and attached to a 1.5-m sampling line from the CO_2 analyzer. (A 16-gauge catheter may be used for endotracheal tubes ≥ 3.5 mm OD).

secretions), it may be necessary to flush the secretions back into the trachea, or, alternatively change tubes. A new endotracheal tube may be problematic if intubation was difficult or if the airway is inaccessible. Sampling with a distal catheter may be impossible if the purge mode of the capnometer is actuated in response to increased resistance to sample flow.

The accuracy of proximally aspirated measurements is improved by inserting a small heat and moisture exchanger (e.g., a miniature Humid-Vent, Gibeck Respi-

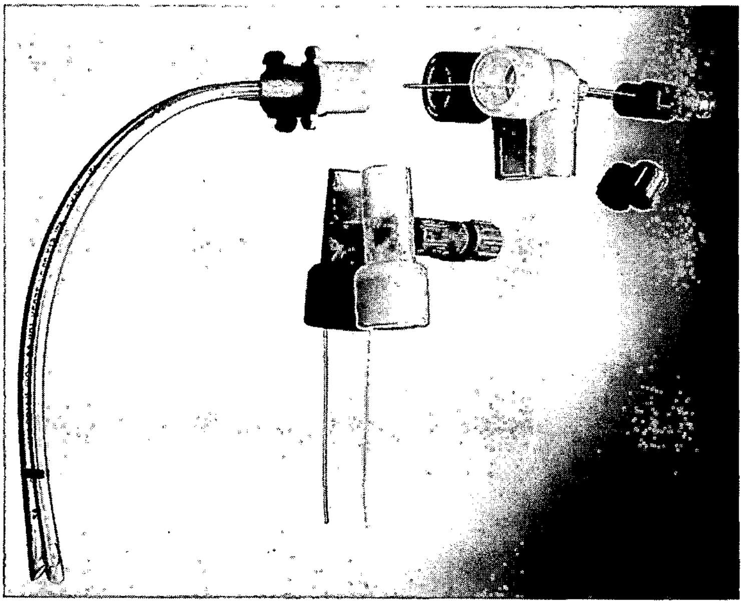

Figure 3. End-tidal Pco_2 may be sampled from approximately the midlength of the endotracheal tube using a 19-gauge Gibeck-Dryden catheter inserted into a clear plastic elbow or a t-piece. (Courtesy of the Gibeck-Dryden Corporation, Indianapolis, Indiana).

ration, Upplands Uäsby, Sweden) between the fresh gas inlet and the tracheal tube connector. The use of such an exchanger, however, may lead to the accumulation of water within the sampling line, which could block the sampling line or damage the capnograph. The use of water filters, traps, and water-permeable sampling lines (e.g., Nafion) can minimize these effects. However, water-permeable catheters have led to incorrect calibration of some CO_2 analyzers.[38] Because the gas is "dried" by these catheters, some manufacturers have recommended that the vapor pressure of water (47 mm Hg) be ignored in the internal calibration. However, if the display value of PCO_2 is internally calculated as dry gas (fractional concentration of CO_2 × barometric pressure) rather than wet gas (fractional concentration of CO_2 × barometric pressure minus 47 mm Hg), a significant error may be introduced.[38]

The sample flow rate for aspirating capnography in infants and children is similar to that used in adults.[17] Sample flow rates of 150 or 240 mL/min do not affect the adequacy of spontaneous[22] or controlled ventilation.[3, 22] For example, in a 3-kg infant ventilated at 30 breaths per minute with an inspiratory to expiratory ratio of 1:1, a sample flow rate of 150 mL/min will only aspirate 2.5 mL from the tidal volume (8% if tidal volume is 10 mL/kg).[17] These sample flow rates will also allow accuracy at higher respiratory rates.[24] For example, when infrared aspiration capnography is used, accuracy is limited to respiratory rates less than or equal to 40 breaths per minute with a 50 mL/min sample flow rate and less than or equal to 75 breaths per minute with a 150 mL/min sample flow rate.[24]

Spontaneously breathing nonintubated patients may be monitored with aspirating capnography by taping the sampling catheter adjacent to the external nares. Although a large difference may exist between arterial and end-tidal CO_2 values due to the large dead space of the face mask and high fresh gas flows, this technique may be used to monitor respiratory trends and to detect airway obstruction.

Accurate Flow-Through Capnography

Flow-through capnography has proved to be accurate in infants and children[3, 20, 21] even at rapid ventilatory rates.[15] There are, however, limitations with some models of the flow-through capnometers. The Seimens-Elema 930 CO_2 analyzer comes with a low dead space pediatric cuvette, but the sensor housing itself is bulky, heavy, and requires heating. Therefore, it may kink or dislodge the tracheal tube or it may cause a burn injury if it contacts skin for an extended period. Furthermore, since this analyzer recalibrates after each breath and assumes the inspired PCO_2 is zero, erroneous estimates of the end-tidal CO_2 may result if rebreathing were present.[2] The Hewlett-Packard 47201A (Hewlett-Packard Co, Waltham, MA) capnograph has proved to be accurate in very small infants, but even the use of a 2-mL dead space sensor (14363A) may increase the PCO_2 in small infants.[21] The Novametrix 1260 capnograph uses an even smaller dead space cuvette (0.6 mL). Furthermore, the Novametrix 1260 sensor (Novametrix Medical System, Inc, Wallingford, CT) is lightweight and well insulated to prevent patient injury. This capnograph accurately estimates the end-tidal CO_2 measurement without affecting the adequacy of ventilation.[3]

Isocapnic Ventilation and Fresh Gas Flow Formulas

In pediatric patients ventilated through a partial rebreathing circuit (e.g., a Mapleson D circuit: Bain or Jackson-Rees) with constant fresh gas flows, inspired CO_2 ($PICO_2$) increases when respiratory rates increase.[6] End-tidal CO_2 does not change despite increasing $PICO_2$ (isocapnic ventilation).[6] Isocapnic ventilation can be explained by the following CO_2 mass balance: $PaCO_2$ or $PETCO_2 = \dot{V}CO_2/\dot{V}_{ALV} + PICO_2$ where $\dot{V}CO_2 = CO_2$ production and $\dot{V}_{ALV}$ = alveolar ventilation. For isocapnic ventilation to occur, i.e., for constant $PETCO_2$ while $PICO_2$ increases, $\dot{V}_{ALV}$ must increase if $\dot{V}CO_2$ remains constant. Such is the case when the respiratory rate increases. Data from a 9.5-kg infant ventilated with an Air-Shields Ventimeter and a Jackson-Rees circuit demonstrate an unchanged distally sampled end-tidal CO_2 despite an increase in the $PICO_2$ due to rebreathing (baseline > 0 mm Hg PCO_2) (Fig. 4).[6] In the upper portion of Figure 4, isopleths of constant end-tidal PCO_2 (30 and 38 mm Hg) were produced by varying fresh gas flow and minute ventilation ($\dot{V}e$). $\dot{V}e$ was varied by changing the respiratory rate and holding tidal volume constant. Note that as $\dot{V}e$ increases on the isopleth, rebreathing increases (points A, B, and G in Fig. 4). Rebreathing does not occur (1) at the point on the isopleth where the fresh gas flow must be increased to maintain a constant $PETCO_2$ (the "elbow") and (2) along the vertical segment of the isopleth. Fresh gas flow requirement (FGFR) formulas for infants and children ventilated through a Mapleson D circuit were derived by defining the horizontal segment of the isopleth as the minimal FGFR for end-tidal PCO_2 of 38 or 30 mm Hg.[6] Averaging the FGFR from 35 infants and children produced two formulas: (1) for an end-tidal PCO_2 of 30 mm Hg, FGFR = 500 mL/kg/min, and (2) for an end-tidal PCO_2 of 38 mm Hg, FGFR = 250 mL/kg/min. When these formulae were applied to another group of infants and children, a wide range of end-tidal PCO_2 values were observed.[6] These data suggest that the adequacy of ventilation in infants and children can only be determined by accurate end-tidal PCO_2 monitoring.

The isopleths of isocapnic ventilation may be very useful to help guide decisions about ventilation in anesthetized infants and children. For instance, the isopleths of isocapnic ventilation may be helpful to interpret recommendations for fresh gas

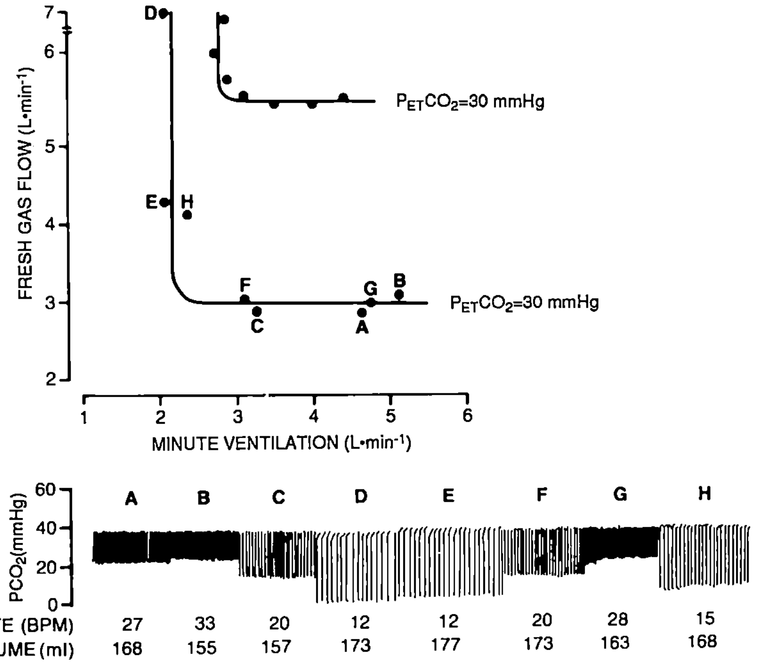

Figure 4. The isopleths for $P_{ET}CO_2$ of 30 and 38 mm Hg and capnographic waveform (at slow paper speed) for $P_{ET}CO_2$ of 38 mm Hg in a 9.5-kg 1-year-old infant. The letters (A–H) on the capnographic waveform correspond to the lettered points (A–H) on the isopleth. See text for explanation. (*From* Badgwell JM, Wolf AM, McEvedy BAB, et al: Fresh gas flow formulae do not accurately predict end-tidal PCO_2 in paediatric patients. Can J Anaesth 35:581–586, 1988; with permission.)

flow (FGF) and $\dot{V}e$. For example, Nightingale et al[26] recommended avoidance of rebreathing by using high FGF and low $\dot{V}e$ (points E and H in Fig. 2). Rayburn and Graves[29] recommended settings that would produce maximal rebreathing, low FGF, and high $\dot{V}e$ (point B in Fig. 2). Rose and Froese[32] suggested that $\dot{V}e$ should be twice the FGF. Our recommendation is to use FGFs as determined previously and to set the $\dot{V}e$ equal to or slightly greater than FGF.[6] Without accurate measurements of tidal volume, how does one estimate $\dot{V}e$ to determine whether $\dot{V}e$ exceeds the FGF? According to the isopleths, $\dot{V}e$ is greater than or equal to FGF when rebreathing is present on the capnogram. The isopleths of isocapnic ventilation may also provide the anesthesiologist with guidelines for appropriate ventilation variables. If hypercapnia is present, one may increase either FGF or $\dot{V}e$. The decision is predicate on the presence or absence of rebreathing. If rebreathing is present, one would increase the FGF, whereas if there is no rebreathing, one would increase $\dot{V}e$. Alternatively, if hypocapnia is present, one would decrease FGF in the presence of rebreathing and decrease $\dot{V}e$ in the absence of rebreathing.

Elevation of the Capnographic Waveform Baseline

Determining the cause of an elevated baseline (FI_{CO_2}) on the pediatric capnogram can be an interesting diagnostic dilemma. Is it true rebreathing? Is it axial diffusion ("slurring") of CO_2 as it travels through the long sampling lines used in aspiration capnography? Is it some other distortion conferred on the capnogram because of the capnometer's slow response to rapid ventilatory rates? Certainly, some rebreathing can occur in infants and children ventilated through Mapleson D breathing systems. The dilemma is to differentiate between rebreathing and distortion (artifact) of the capnogram.

It has been suggested that in pediatric patients with rapid ventilatory rates, plugs of CO_2 mix in the long sampling catheters thereby distorting the capnographic waveform (poorly defined upstroke and downstroke and elevated baseline) (Fig. 5).[16] The nature of mixing of CO_2 plugs in these patients is unclear. In a mathematical

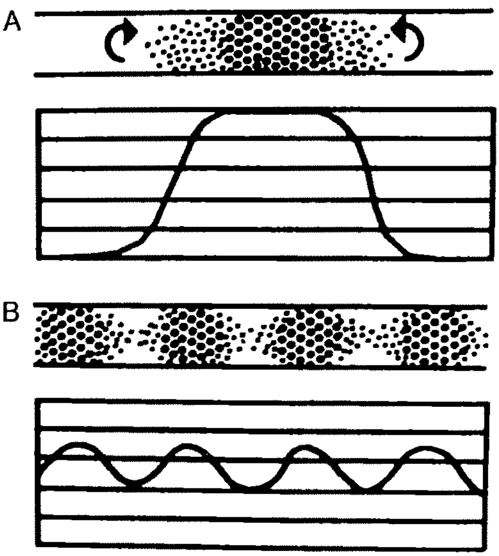

Figure 5. A plug of CO_2 (stippled area) in a sampling catheter. Below the sampling catheter is the capnogram that would result if this plug reached a CO_2 analyzer. (*A*) As long as the front and back of the plug are well defined, the resultant capnogram will have a sharp upstroke and downstroke and the baseline will return to zero. (*B*) Several CO_2 plugs (as may occur in infants with rapid ventilation measured in a long sampling catheter) follow each other resulting in a capnographic waveform with poorly defined upstrokes and downstrokes and an elevated baseline. This phenomenon would lead to an artifactual elevation of the baseline of the capnogram. (*From* Gravenstein JS, Paulus DA, Hayes TJ: Carbon Dioxide and Monitoring in Capnography in Clinical Practice. Boston, Butterworth; 1989, p 9; with permission.)

model of catheter sampling systems, Epstein et al[14] calculated that molecular axial diffusion could be neglected when Schmidt's number (a dimensionless number relating viscosity and density as an index of the diffusibility of gases) is greater than 0.43. The Schmidt's number of CO_2 in air is 1.2, suggesting that molecular axial diffusion does not occur.[14] However, there is evidence to suggest that mixing of gases does indeed occur in very long sampling catheters used by some mass spectrometers. In a study of the frequency response of long mass spectrometry sampling catheters, Scammon[34] observed a 10% error in the inspired CO_2 using a 210-foot sampling catheter when respiratory frequency was 40 breaths per minute. During controlled ventilation of infants (respiratory rates = 6–70 breaths per minute) monitored with aspiration of gases for mass spectrometry (sampling catheter length = 30 m, sample flow rate = 240 mL/min), artifactual increase in $PICO_2$ contributed 0% to 25% of the capnographic baseline depending on respiratory rate (Fig. 6).[4a] One explanation for these findings is that parabolic distortion of the CO_2 plug occurs as it traverses the long sampling catheter. Parabolic distortion may be caused by mechanical aspects of laminar flow (slower movement of gas near the catheter wall due to increased friction), thereby producing partial fusion of CO_2 plugs. This is different from molecular axial diffusion, which apparently does not occur.[14]

Elevation of the capnographic baseline may also occur as a result of the capnometer's slow response time. The response times of the capnometer are transit time, rise time, and total delay time. Transit time is the time for a sample of gas to travel from the sampling site through the sample catheter to the analyzer. The transit time depends on the length and diameter of the sample catheter and the rate at which gas is aspirated. Rise time is unaffected by sample catheter length and is defined as the time taken for the analyzer output to respond to a sudden step change in CO_2 concentration—the time it takes for the analyzer output to change from 10% of the final value to 90% of the final value. CO_2 measurements are not accurate if the response time of the CO_2 analyzer is too slow and its output fails to reach the actual CO_2 concentration at the end of the breath. Total delay time is the rise time plus the transit time. If the total delay time exceeds the respiratory cycle time (the time for one breath), the analyzer will display a spuriously low end-tidal CO_2 and high baseline (inspired) CO_2.[36]

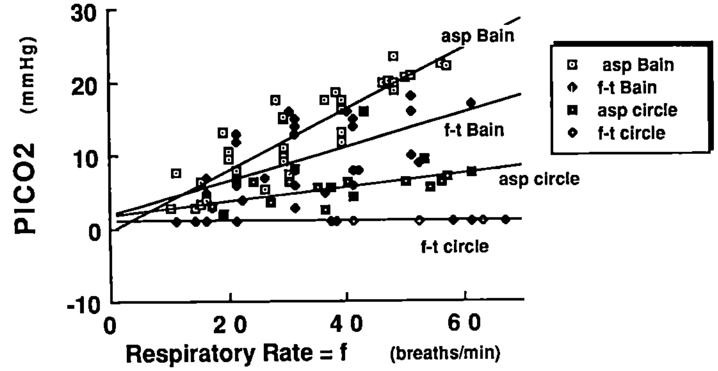

Figure 6. Inspired PCO_2 ($PICO_2$) measured by aspiration (asp) or flow-through (f-t) capnography plotted versus respiratory rate in infants ventilated through either a Bain or semiclosed circle breathing system. The asp Bain line represents rebreathing plus artifact, the f-t Bain line represents rebreathing alone, the asp circle line represents artifact alone, and the f-t circle line represents non-rebreathing. (*From* Badgwell JM, Kleinman SE: Does axial dispersion of carbon dioxide occur in the long sampling lines used in pediatric capnography? Can J Anaesth 38:A144, 1991; with permission).

Awareness of the potential for artifactual changes in the capnogram will avoid their misinterpretation as physiologic events. With the caveat that an elevated baseline may contain 10% to 25% error (at very high respiratory rate) due to artifact, rebreathing may still be used as a helpful guide in delivering ventilation to infants and children (see previous discussion).

Waveform Interpretation

In children and adults ventilated through a semiclosed circle system with a CO_2 absorber, the normal capnographic waveform includes a return to zero baseline. The normal pediatric capnogram (like the waveform in adults) includes a sharp upstroke as alveolar gas displaces tracheal gas and a slightly ascending plateau phase. Significant deviations from this morphology suggest an abnormality in the patient, the gas delivery system, or the sampling technique.

Esophageal intubation is diagnosed by the absence of a waveform or a waveform with small rounded humps of decreasing height. Since the stomach could contain some CO_2 after a mask induction, more than one breath should be observed to confirm tracheal tube placement. For instance, when single-use color indicator devices are used to detect CO_2, six breaths are recommended to confirm tracheal placement. Bronchial intubation may initially give normal or slightly lower end-tidal PCO_2 measurements (Fig. 7). If, however, the bronchial placement is allowed to persist for a period of time, and the lungs are hypoventilated, end-tidal PCO_2 may increase (Fig. 8).[5] Changes in the capnographic waveform are not diagnostic of a specific disorder. For instance, a sloping expiratory upstroke may indicate a kinked endotracheal tube or airway obstruction (e.g., bronchospasm).

A sudden disappearance of the capnogram indicates complete obstruction, breathing circuit disconnection, or a precipitous increase in dead space (pulmonary embolus or cardiac arrest). A decrease in end-tidal CO_2 to a low but measurable value may occur in the presence of an excessive leak around the endotracheal tube. In this case, the fresh gas flow replaces alveolar gas, thereby diluting the exhaled gas. A gradual decrease in the end-tidal CO_2 may reflect alveolar hyperventilation or pulmonary hypoperfusion (Fig. 9). A slowly increasing end-tidal CO_2 may occur with alveolar hypoventilation or in circumstances in which the CO_2 production

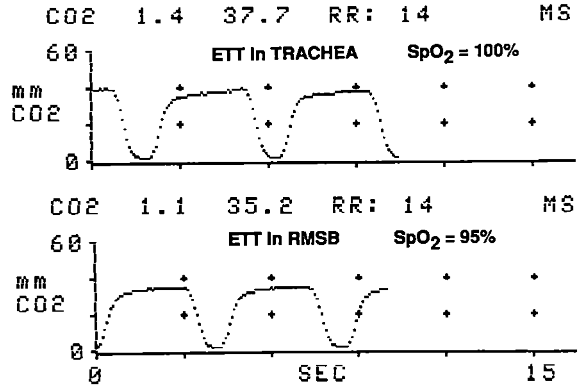

Figure 7. The capnographic waveform measured by mass spectrometry from a 15-kg 18-month-old child ventilated with an Ohmeda 7810 ventilator and a semiclosed circle breathing system (Ohmeda, Madison, WI). When the endotracheal tube (ETT) was advanced from the trachea into the right main stem bronchus (RMSB) end-tidal PCO_2 decreased from 37.7 mm Hg to 35.2 mm Hg, and oxygen saturations decreased from 100% to 95% (unpublished data).

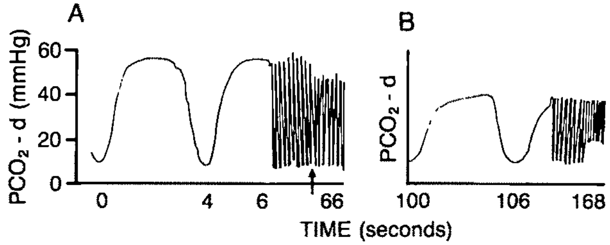

Figure 8. (*A*) Capnographic waveform obtained from the distal end of the endotracheal tube and measured by infrared analysis in an 18-kg 4-year-old child ventilated with an Air-Shields Ventimeter. After 20 minutes of controlled ventilation, endobronchial intubation was diagnosed and treated. (*B*) After correct placement of the endotracheal tube (denoted by arrow in A) end-tidal P_{CO_2} returned to normal. (*From:* Badgwell JM, McLeod ME, Lerman J, et al: End-tidal P_{CO_2} measurements sampled at the distal and proximal ends of the endotracheal tube in infants and children. Anesth Analg 66:959–964, 1987; with permission from the International Anesthesia Research Society.)

increases. A very rapid and large increase in the end-tidal CO_2 may suggest malignant hyperthermia. A gradual rise in both inspired and end-tidal CO_2 in a patient ventilated with a circle circuit may indicate faulty inspiratory or expiratory valves. Idiosyncratic inspiratory "bumps" occur when using the Sechrist Infant Ventilator (Fig. 10). Cardiac oscillations occur in children with slow respiratory rates and can be differentiated from "curare clefts" by comparing heart rates to the frequency of waveform oscillation (Fig. 11).

Physiology of Plateaus and Arterial to End-Tidal CO_2 Differences

The presence of a plateau on the capnographic waveform does not always indicate that the end-tidal CO_2 value reflects the arterial CO_2 value (Fig. 12).[4, 14] A flat plateau in the presence of a large arterial to end-tidal difference may occur in patients with large dead space ventilation (e.g., bronchopulmonary dysplasia) and in small infants when proximal sampling is used inappropriately.[4] When accurate sampling is available in anesthetized, intubated, ventilated infants and children,

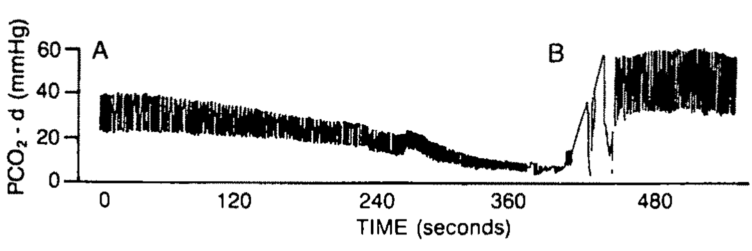

Figure 9. Capnographic waveform obtained from the distal end of the endotracheal tube in a 10-kg 1-year-old infant with systemic hypotension that occurred during controlled ventilation with 2% halothane and 70% N_2O/O_2. (*A*) The waveform shows a gradual but profound decrease in $P_{ET}CO_2$ suggesting decreased pulmonary blood flow and CO_2 delivery to the lungs. (*B*) Discontinuation of halothane and the administration of 100% oxygen was associated with a restoration of normal blood pressure and the return of end-tidal P_{CO_2} to above normal values. (*From* Badgwell JM, McLeod ME, Lermon J, et al: End-tidal P_{CO_2} measurements sampled at the distal and proximal ends of the endotracheal tube in infants and children. Anesth Analg 66:959–964, 1987; with permission from the International Anesthesia Research Society.)

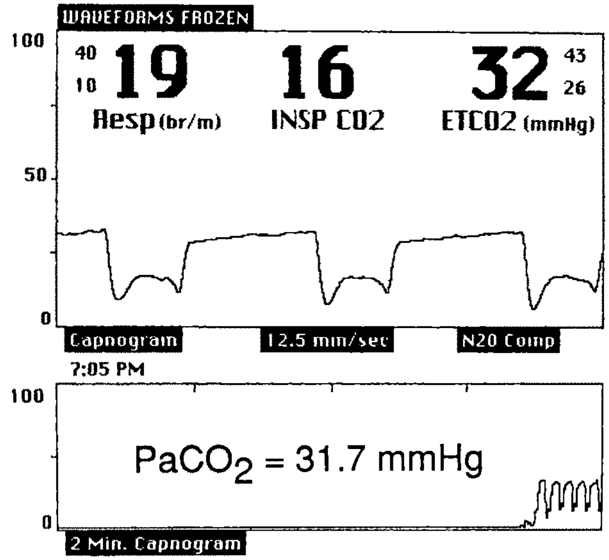

Figure 10. Capnographic waveform measured by flow-through capnography from an 8.1-kg 10-month-old infant ventilated with a Sechrist Infant Ventilator. The humps that occur during the inspiratory phase are idiosynchratic for the Sechrist Ventilator and do not affect the adequacy of ventilation (unpublished data). Resp (br/m), respiratory breaths per minute, Insp, inspiratory, end-tidal CO_2, nitrous oxide compensation.

the arterial to end-tidal P_{CO_2} differences are either small, negligible, or possibly of negative value.[3-5] These data suggest that dead space ventilation is minimal in these patients.

Some clinicians have suggested that capnography is accurate in the absence of a plateau phase. In one study, distally sampled peak expired P_{CO_2} estimated Pa_{CO_2} despite the lack of a plateau phase during expiration.[22] Peak expired P_{CO_2} was accurate in controlled and spontaneously ventilated critically ill neonates when the respiratory rate was less than 70 breaths per minute and when lung disease was not

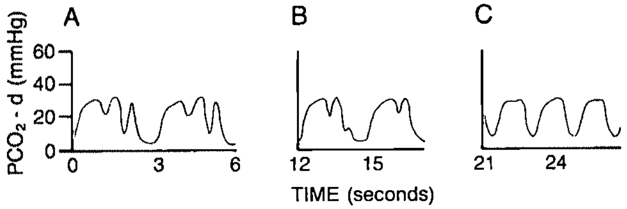

Figure 11. *A*, Capnographic waveform obtained from the distal end of the endotracheal tube in a 5-kg 4-month-old infant after partial recovery of neuromuscular function and attempts by the infant to breathe spontaneously. (*B*, *C*) After increasing the inspired concentration of halothane from 0.5% to 1.0% and the respiratory rate from 18 to 36 breaths per minute, the "curare cleft" resolved. (*From* Badgwell JM, McLeod ME, Lerman J, et al: End-tidal P_{CO_2} measurements sampled at the distal and proximal ends ot the endotracheal tube in infants and children. Anesth Analg 66:959–964, 1987; with permission from the International Anesthesia Research Society.)

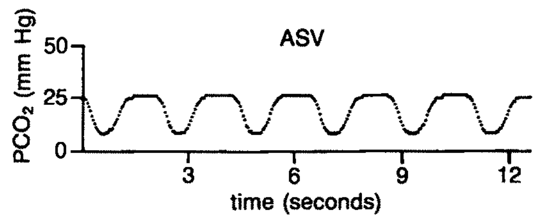

Figure 12. Capnographic waveform showing the plateau phase in a 4.1-kg 2-month-old infant ventilated with an Air-Shields Ventimeter and a Bain circuit with a fresh gas flow of 1.4 L/min, respiratory rate of 32 breaths per minute, and inspiratory to expiratory ratio of 1:2.33. $Paco_2$ = 40.3 mm Hg, $P_{ET}CO_2$ = 26.4 mm Hg, and the difference between $Paco_2$ and $P_{ET}CO_2$ = 13.9 mm Hg. (*From* JM Badgwell, JE Heavner, WS May, et al: Anesthesiology 66:405–410, 1987; with permission.)

severe (i.e., when the FIo_2 was < 0.7).[22] Others have reported anecdotally that peak expired CO_2 values may be low in rapidly and spontaneously ventilating infants and that peak expired CO_2 values increase markedly when CO_2 is "squeezed out" by manual compression of the chest in these infants.

In infants and children with acyanotic congenital heart disease, end-tidal Pco_2 measurements are a reliable estimate of arterial Pco_2.[10] However, in infants and children with cyanotic congenital heart disease, end-tidal Pco_2 may not reliably estimate arterial Pco_2.[10] In the latter group, both dead space ventilation and venous admixture (Qs/Qt) increase the difference between arterial and end-tidal Pco_2.[10] Increasing the Qs/Qt ratio increases the Pco_2 difference by shunting venous blood to the left side of the heart with a greater Pco_2 tension than that in the alveoli.

THE RELATIONSHIP OF CAPNOGRAPHY AND PULSE OXIMETRY

Pulse oximetry and capnography together provide continuous monitoring of oxygenation, ventilation, and tissue perfusion. In the child with a decreasing cardiac output, the capnographic waveform may diminish (gradually or suddenly, depending on the rate of cardiac collapse) along with the simultaneous failure of pulse oximetry. The presence or absence of blood pressure and pulses will quickly confirm capnographic and oximetric evidence of a decreasing cardiac output.

Pulse oximetry reduces both the frequency and severity of hypoxemic events during anesthesia in children.[12] In a comparative study with capnography, Rolf et al[31] noted that oximetry was more likely to detect episodes of hypoxemia. This is not surprising in view of the nature of these monitors. Before the onset of arterial hemoglobin oxygen desaturation, capnography may provide an early warning of ventilation mishaps that could cause significant morbidity (e.g., esophageal intubation and disconnections).[31] It is noteworthy that in this study, the anesthesiologist did not respond to changes in the capnograph until arterial hemoglobin oxygen desaturation confirmed the potential ventilation mishap.[31] The authors concluded that oximetry is superior to capnography in providing an early warning sign of events that can cause hypoxemia.[31] Nevertheless, capnography does have a very important role in preventing ventilation mishaps that could result in hypoxemia.

SUMMARY

Perioperative morbidity and mortality are greatest in childhood. This has been attributed to a large extent to perioperative hypoxic events. The introduction of pulse oximetry and capnography into pediatric anesthetic practice has dramatically decreased the frequency of hypoxic events and airway mishaps. Indeed, these monitors have proved to be more sensitive at detecting adverse events than has our clinical acumen. Since oximetry and capnography have become minimum standards for anesthetic care, it is my belief that perioperative morbidity and mortality will decrease. The inclusion of these two monitors in pediatric care may be the most important contributions to monitoring since the precordial stethoscope.

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Regional Anesthesia

*Raafat S. Hannallah, MD**

Regional blocks can be combined with light general anesthesia to provide excellent postoperative pain relief and early ambulation with minimal or no narcotics. [19] Regional blocks can be especially advantageous in ambulatory surgery.[13] A block can be performed at the end of surgery to obtain the maximum duration of analgesia in the postoperative period. However, for shorter procedures and with the availability of longer-acting local anesthetics (e.g., bupivacaine), there may be a further advantage in placing the block before surgery starts, but after the child has been anesthetized.[20] This may help reduce the requirement for general anesthetic agents during surgery and thereby lead to a more rapid recovery, earlier discharge, return of normal appetite, and less nausea and vomiting.

The types of blocks that can be safely used in the pediatric surgical patient are limited only by the skill and interest of the individual anesthesiologist. The techniques chosen should be simple and expedient, have minimal or no side effects, and should not interfere with motor function and early ambulation. Bupivacaine, which offers the distinct advantage of a long duration of action, has been extensively used in pediatric anesthesia at our institution as well as many others in a dose range of 2 to 3 mg/kg. The following are among the regional blocks widely used today in pediatric patients.

ILIOINGUINAL AND ILIOHYPOGASTRIC NERVE BLOCK

This simple block produces effective postoperative pain relief following outpatient hernia repair in children.[22] It also can be used for other procedures that require an inguinal incision, such as hydrocelectomy and orchiopexy.[12]

The ilioinguinal nerve runs between the transverse and internal oblique muscles. The iliohypogastric nerve runs superficial to the inguinal muscles close to the anterior superior iliac spine. Both nerves can easily be blocked by infiltration of the abdominal wall in the area medial to the anterior superior iliac spine[22] (Fig. 1). A 25-gauge needle is used to puncture the skin 1 cm medial and 1 cm

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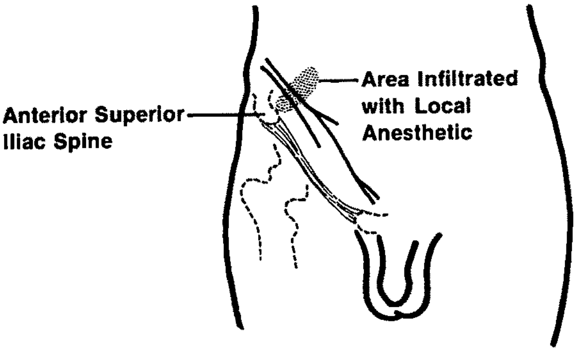
Anterior Superior Iliac Spine
Area Infiltrated with Local Anesthetic

Figure 1. Ilioinguinal and iliohypogastric nerve blocks are performed by infiltrating the abdominal wall muscle medial to the anterior superior iliac spine. (*From* Hannallah R, Epstein B: The pediatric patient. *In* Wetchler BV (ed): Anesthesia for Ambulatory Surgery, ed 2. Philadelphia, JB Lippincott, 1991; with permission.)

inferior to the anterior superior iliac spine, just above the inguinal ligament. Three fan-shaped injections, plus a subcutaneous wheal, are made as the needle is withdrawn. If the block is performed at the completion of surgery, the area to be infiltrated may be approached through the lateral edge of the groin incision.[12]

Shandling and Steward[22] used 0.5% bupivacaine in a dose of up to 2 mg/kg with 1:200,000 epinephrine to perform the block in 81 children undergoing elective inguinal herniotomy. The blocks were performed following the induction of general anesthesia and before the start of surgery. The time required for the surgeon to complete the block was approximately 60 seconds. Only 3 of the 81 children who received the block, compared with 74 of 75 control patients, required additional analgesics in the postanesthetic recovery area. At home, analgesics were given by the parents to 32 of 75 children in the control group and to 24 of 81 children who had received a nerve block. Return to a bright and alert status and normal activity occurred significantly more rapidly in those children who had received the nerve block compared with the control patients. Both groups had a similar incidence of nausea and vomiting. The only observed complication was a transient motor block of the femoral nerve that caused three patients to have short-lived difficulty with walking. This probably occurred because the local anesthetic solution had reached the femoral nerve by tracking within fascial planes. In a study at Children's National Medical Center, we used a more dilute bupivacaine solution (0.25%) to perform the block and noted no such complication.[12] In that study, which involved children undergoing orchiopexy on an outpatient basis, the blocks were performed before closing the incision. Using an objective scale, postoperative pain and discomfort in children receiving regional nerve blocks, caudal blocks, and no blocks were compared. Both groups of patients receiving blocks showed significantly better postoperative pain relief than the controls.[12]

When a 2 mg/kg dose of bupivacaine was used to perform the block in a recent study, the mean peak plasma level was 1.35 ± 0.35 μg/mL, well below the potentially toxic level of 4 μg/mL. Maximum plasma bupivacaine concentrations were observed between 10 and 40 minutes following block placement.[9]

Casey et al[7] have recently described a simpler approach to blocking the ilioinguinal and iliohypogastric nerves in the inguinal canal. These authors found that simple irrigation of the hernia wound before surgical closure with a 0.25 to 0.5 mL/kg solution of 0.25% bupivacaine was as effective as the previously described method. The so-called "instillation block" presumably works by blocking the nerve bundles and branches that are exposed during the surgical dissection of the hernia sac.

NERVE BLOCKS OF THE PENIS

Block of the dorsal nerves of the penis provides effective analgesia for hypospadias repair and circumcision, both of which are commonly performed in pediatric ambulatory patients.

The distal two thirds of the penis is innervated by the dorsal nerves, which are bilateral and adjacent to the midline. The dorsal nerves are distal branches of the pudendal nerves, which arise from the sacral plexus (S2–4). At the base of the penis, they divide into multiple filaments that encircle the shaft before reaching the glans. They are covered by Buck's fascia and lie beside the paired dorsal arteries and single vein of the penis as well as midline structures. The base and proximal part of the penis are innervated by the genitofemoral and ilioinguinal nerves.

Two techniques have been described for placing a penile block (Fig. 2).

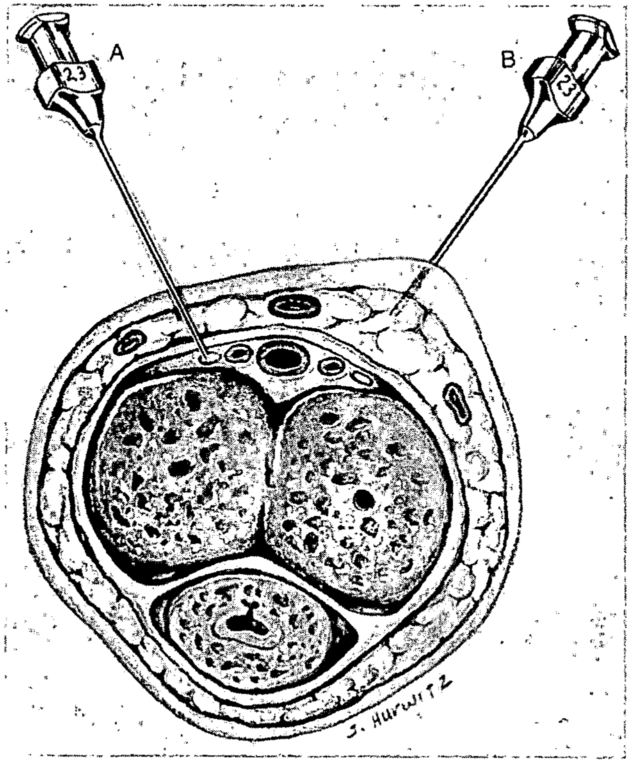

Figure 2. *A*, Dorsal nerve vs. *B*, ring block of the penis. Note the position of the needle in relation to Buck's fascia in each case. (*Modified from* Hannallah R, Epstein B: The pediatric patient. *In* Wetchler BV (ed): Anesthesia for Ambulatory Surgery, ed 2. Philadelphia, JB Lippincott, 1991; with permission.)

Broadman et al[3] used the subcutaneous ring block, consisting of subcutaneous infiltration with 0.25% bupivacaine. The second method, dorsal penile nerve block, involves injection at the 10:30 and 1:30 clock positions of 1 to 2 mL of local anesthetic deep to Buck's fascia. One or two injections are made for each of the paired nerves.[24] This technique was found to provide good analgesia in 96% of cases. In a more recent study, dorsal nerve block was found to provide good pain relief following circumcision. Analgesia in nerve block patients tended to be of shorter duration than that resulting from caudal block[28]; however, children in the former group micturated and stood unaided earlier and had a lower incidence of vomiting than those who received a caudal block. Epinephrine-containing solutions must never be used to block the penis, as it is an end organ and vasoconstriction may seriously compromise its circulation.

Topical lidocaine also has been successfully employed to produce penile analgesia following circumcision in children. In two recent studies, lidocaine spray, ointment, or jelly was found to be effective in reducing pain and avoiding the need for postoperative analgesics.[26, 27] Lidocaine jelly also proved to be an effective postdischarge treatment for such pain.

CAUDAL BLOCK FOR POSTOPERATIVE ANALGESIA

Caudal analgesia is the most useful and popular pediatric regional block used today. It is simple to perform and easily adaptable to ambulatory anesthesia practice. "Sacral segment" procedures such as circumcision, hypospadias repair, anal surgery, and clubfoot repair are common indications for caudal blocks at Children's National Medical Center. In these patients, the caudal block greatly reduces the risk of reflex laryngeal spasm in response to surgical stimulation and may, therefore, remove the need for endotracheal intubation.

The sacral hiatus, which is situated at the lower end of the sacrum, is extremely easy to identify in infants and young children. Its existence is due to the nonfusion of the fifth sacral vertebral arch. The large bony processes on each side are called the *cornua.* The coccyx lies immediately caudal to the sacral hiatus. The hiatus is covered by the sacrococcygeal membrane. In infants and prepubertal children, these landmarks are easily palpable or even visible through the skin because of the absence of the large sacral pad of fat that usually develops at puberty. The dural and arachnoid sacs may extend to the third or fourth sacral vertebra in infants. In addition, the sacral hiatus is relatively more cephalad in infants; thus, the distance between the sacral hiatus and the end of the dural sac is relatively short (Fig. 3).

The lateral position is most often employed to perform a caudal block in children. To identify the sacral hiatus, one begins by palpating the tip of the coccyx (lowest bony part of the spine). With the left index finger applying firm pressure to identify the coccyx, one moves the finger gently from side to side and proceeds in a cephalad direction. The first double bony protuberances encountered are the two cornua of the sacrum that define the sacral hiatus. The cornua should be marked either mentally or with a skin-marking pen.

After careful skin preparation, the sacral hiatus is again identified using firm pressure by the left index finger. Asepsis is maintained either by gloving or by palpating the skin through a sterile alcohol swab (Fig. 4). The caudal space is entered using a short (1-inch) 23-gauge needle that has been attached to a syringe containing the appropriate volume of local anesthetic solution. The needle must be placed exactly in the midline and inserted at a 60 degree angle to the coronal plane, perpendicular to all other planes. As the needle is advanced, the bevel should be facing anteriorly to minimize the chance of piercing the anterior sacral wall (the most common reason for aspirating blood). A distinct pop is felt as the sacrococcygeal

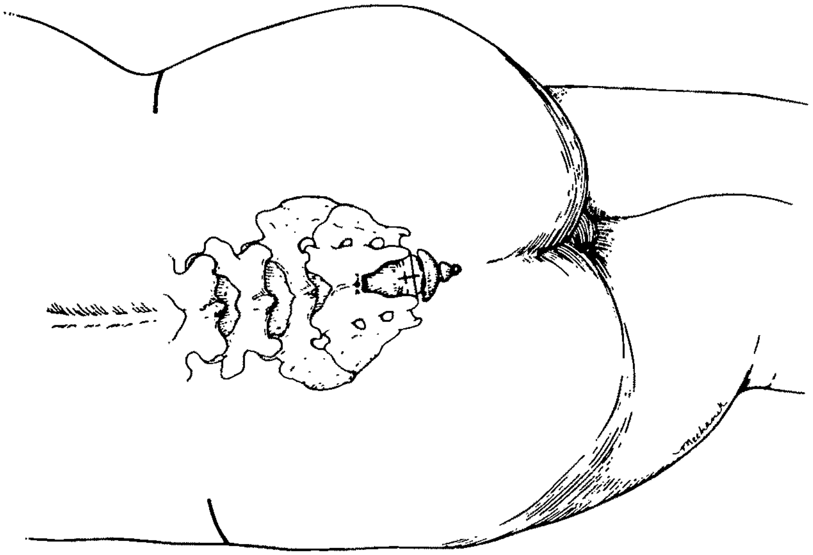

Figure 3. The sacral hiatus is relatively more cephalad in infants. (*From* McClain B: Pediatric Caudal Anesthesia, Medical College of Georgia, Augusta, 1990; with permission.)

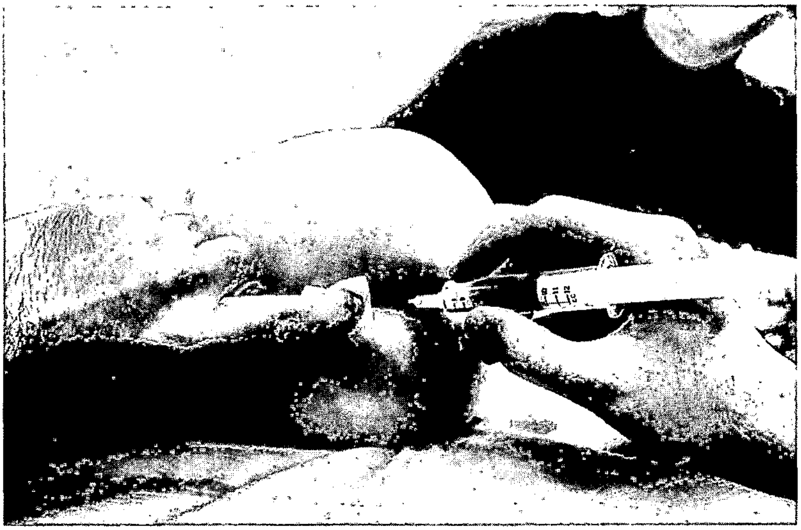

Figure 4. Strict aseptic techniques are essential during caudal block placement. Either a nontouch method (as shown) or gloving is acceptable. (From Hannallah R, Epstein B: The pediatric patient. *In* Wetchler BV (ed): Anesthesia for Ambulatory Surgery, ed 2. Philadelphia, JB Lippincott, 1991, with permission.)

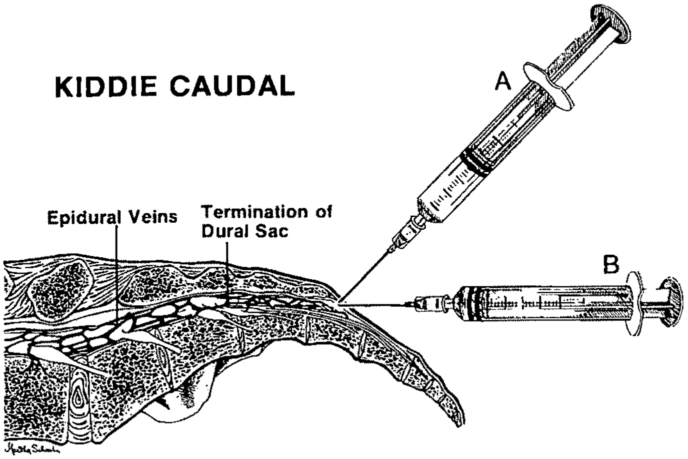

Figure 5. *A* and *B*, Needle placement and advancement through the sacrococcygeal membrane. The bevel is facing anterior to avoid intraosseous introduction. (*From* Broadman LM: Regional anesthesia for the pediatric outpatient. Anesth Clin North Am 5:53, 1987; with permission.)

membrane is pierced. The angle of the needle is then lowered to 20 degrees and advanced an additional 2 to 3 mm to make sure that all of the bevel surface is in the caudal space (Fig. 5). Further advancement of the needle is not necessary and will increase the chances of dural puncture. After no blood or cerebrospinal fluid is found following repeated aspirations, the appropriate amount of local anesthetic is injected, and the child is placed in a supine position.

In patients less than 4 years of age, the caudal space may also be entered by inserting the needle through the cartilaginous back of the third or fourth sacral vertebral arch. This approach is particularly useful in the rare instances when the sacral hiatus is difficult to identify. To avoid dural puncture with this approach, the needle must remain perpendicular to the skin in all planes and should not be advanced any more than absolutely necessary.

Three important variables determine the quality, duration, and extent of a caudal block. These are the volume, total dose, and concentration of the drug. There is currently no general agreement, however, on whether age or weight is the better criterion for achieving the desired level of analgesia in children.

Schulte-Steinberg and Rahlfs[21] examined the statistical significance of age, weight, and height on dose requirements for caudal anesthesia. They found the pattern of spread to be highly predictable in children and further determined that it relates very nicely to age. Using 1% lidocaine or 0.25% bupivacaine solutions, they found that a volume of approximately 0.1 mL per segment per year of age was effective in prepubertal children. The relationship between age and dose requirement is strictly linear, and there is a high degree of correlation up to the age of 12 years.

Takasaki and colleagues[25] studied the dose requirements for caudal anesthesia in a large series of infants and children. They reported that for patients ranging in age from newborn to 7 years, segmental dose requirements correlated better with body weight than with age. Using 1% lidocaine with epinephrine 1:200,000, they recommended calculating the volume of local anesthetic needed per segment as follows: milliters per segment = 0.056 × body weight (kilograms).

In clinical practice, we find the most workable formula is that suggested by

Armitage.[2] Using the desired local anesthetic solution, Armitage maintains that a volume of 0.5 mL/kg will result in an adequate sacral block. One milliliter per kilogram is used to block the lower thoracic nerves; 1.25 mL/kg is needed to reach the midthoracic region. The total dosage should always be checked to ensure that it is within the acceptable safe limit.

Eyres et al[10] measured plasma bupivacaine concentrations following caudal injection of 3 mg/kg of 0.25% bupivacaine solution in 45 children whose ages ranged from 4 months to 12 years. They found mean blood levels ranging from 1.2 to 1.4 μg/mL, which are well below the projected toxic levels in adults.

The results of using different bupivacaine concentrations on the quality of a caudal block have been recently studied. Broadman et al[5] found that 0.3% and 0.375% bupivacaine solutions offered no advantage over the standard 0.25% concentration. On the other hand, Wolf et al[31] reported that a 0.125% bupivacaine solution produced the same quality and duration of postoperative analgesic as a 0.25% concentration. Moreover, the more dilute solution resulted in less motor blockade.

Bromage[6] studied the duration of caudal analgesia in children by recording the time that elapsed before the block level began to recede by at least two spinal segments. When bupivacaine alone was used, it took 2 hours; if an epinephrine-containing solution was used, it was slightly longer. Bromage[6] also noted that the total duration of action in the lower sacral segments was considerably longer than the time that elapsed before the beginning of recession. This observation correlates well with clinical experience, where bupivacaine caudal analgesia, as judged by the time elapsing before the child requires supplemental analgesia, may persist for more than 5 hours.[29]

Caudal blocks in children are usually combined with a light general anesthetic. When short surgical procedures (<1 hour) are performed, the duration of postoperative analgesia is not affected by whether the block is placed before or after surgery.[20] The former approach is preferred, since it reduces the intraoperative need for potent inhalation agents and still ensures excellent postoperative pain relief.

The duration of postoperative analgesia following a caudal block can be substantially prolonged by using preservative-free morphine. In a controlled study involving 22 children, Jensen[14] found that the duration of pain relief was substantially longer with caudal morphine (range, 10–36 hours) than with bupivacaine (range, 4–8 hours). Although there were no complications in these patients, the author cautions that there may be a risk of respiratory depression after administration of epidural morphine. Jensen recommends that no child should be permitted to leave the hospital within 24 hours of receiving a caudal block with morphine. More recently, Krane et al[16] reported good pain relief in a study comparing caudal morphine, caudal bupivacaine, and intravenous morphine for postoperative pain relief following genitourinary or lower extremity orthopedic surgery. Krane[15] also reported delayed respiratory depression requiring naloxone infusion in a 2½-year-old boy who received a caudal dose of 0.1 mg/kg of preservative-free morphine. We continue to avoid, and cannot recommend, the use of caudal narcotics in our ambulatory patients.

Although clinical experience with pediatric caudal block is extensive, reports of large series have been published only recently. Broadman et al[4] reported no complications or toxic reactions associated with caudal blocks in a prospective study of 1154 children. The authors stressed that the key to the safety of the procedure is knowledge of the anatomy in children, meticulous attention to the detail in site selection and preparation, and careful aspiration before drug injection. Dalens and Hasnaoni[8] found no major complications or neurologic sequelae and good patient and parental acceptance in 750 consecutive patients.

The possibility of intraosseous injection must always be considered when performing caudal blocks in children. The cancellous mass of sacral bone is covered by a wafer-thin, brittle layer of cortex that can be easily damaged. Intraosseous penetration is suggested by the appearance of a gritty aspirate in a small volume of apparently pure blood following aspiration. This complication is best avoided by inserting the needle in the line of the sacral canal, avoiding excessive force, and keeping the bevel of the needle directed anteriorly so that it slides over, rather than penetrates, the anterior plate of the sacrum.

Intravenous injection can be prevented by repeated gentle aspiration following each needle movement. If excessive force while attempting aspiration has caused collapse of the veins, no blood may appear. We have found that most bloody aspirates are caused by intraosseous rather than intravenous placement of the needle. In either case, it is our practice to reposition the needle and inject serially 0.5 mL of the solution with reaspiration until blood staining is slight or absent. Matsumiya and coworkers[17] have recently reported a case of cardiovascular collapse in an infant after caudal anesthesia with a lidocaine-epinephrine solution. They attributed the problem to an inadvertent intravascular injection. Although other factors may have played a role in that case (e.g., hypoventilation, overdose of halothane, or both) such reports heighten our awareness of the possibility of such complications.[18]

SPINAL ANESTHESIA FOR HIGH-RISK NEONATES

Spinal anesthesia can be safely and reliably performed in infants and children, including high-risk neonates. The technique may be particularly useful in patients in whom one wishes to avoid general anesthesia or endotracheal intubation, such as former preterm infants or children who have recently undergone tracheal reconstruction.

Many reports have described satisfactory experience with spinal anesthesia in high-risk former preterm infants.[1] It has not been demonstrated, however, in a large prospective, controlled study that these high-risk neonates are less likely to develop apnea or bradycardia when spinal rather than general anesthesia is selected.

In a recent prospective study using pneumography, Welborn et al[30] compared the effects of spinal versus general anesthesia on the incidence of postoperative apnea in 36 former preterm infants. None of the infants who received unsupplemented spinal anesthesia developed apnea, compared with 31% of those undergoing general anesthesia. When spinal anesthesia was supplemented with 1 to 2 mg/kg of intramuscular ketamine, postoperative apnea occurred in 89% of the patients. The authors continue to recommend postoperative monitoring for apnea in high-risk infants, regardless of the anesthetic technique.

Spinal taps are easy to perform in infants. The patient is usually positioned on his or her side, with the back flexed and the neck extended. Since the spinal cord extends lower in infants than in adults, the lumbar puncture is performed at the L4-5 or L5-S1 level, usually with a 22-gauge, 1½-inch spinal needle.

Abajian et al[1] recommend that the needle be left in position for 5 seconds after the local anesthetic has been injected to prevent the drug from tracking back to the site of skin puncture after removal of the needle. Once the needle is removed, the patient is placed in the supine position. Care is taken not to place the feet higher than the head; e.g., one should not immediately lift the infant's legs to place an electrocautery grounding pad on his or her back. Motor blockade should be evident within 1 to 2 minutes. Since patients less than 5 years of age show little or no change in blood pressure with spinal anesthesia, even without fluid loading, we usually place the intravenous catheter in a lower extremity after the spinal anesthetic has been administered rather than struggle with venipuncture to administer fluids before spinal anesthesia is established.

Tetracaine, 0.6 to 0.8 mg/kg in an equal volume of 10% dextrose and a "wash" of epinephrine, is our drug of choice. This mixture produces between 60 and 80 minutes of surgical anesthesia.

A spinal anesthetic does not provide motor control of the upper extremities, and a crying infant with arms waving is not conducive to surgery even if the anesthetic level is adequate. Therefore, appropriate sedation and upper extremity restraints are important parts of this anesthetic technique. Often a soothing touch and a pacifier (whiskey nipple) are all that is needed to keep the infant quiet. It is useful to place the cuff of the blood pressure apparatus on the calf to avoid arousing the infant every time a measurement is taken. Sedation with intravenous ketamine (0.5–1.0 mg/kg) or methohexital (0.5–1.0 mg/kg) may be useful in full-term infants who are no longer at risk for postoperative apnea.

INTRAVENOUS REGIONAL ANESTHESIA

Although it is possible to employ intravenous regional anesthesia on the lower as well as the upper extremities, there are no reports of lower extremity intravenous regional anesthesia in the pediatric patient. However, it has often been employed in the upper extremity in children for the setting of simple forearm fractures.[11]

With the patient supine, a double pneumatic tourniquet of appropriate size is placed on the affected extremity. A 20- to 22-gauge plastic cannula (or 19- to 25-gauge butterfly needle) is inserted into a vein close to the operative site. The extremity is elevated for 3 minutes or exsanguinated with an Esmarch bandage, and the proximal cuff is inflated to approximately 50 mm Hg above the measured systolic pressure. Four milligrams per kilogram of 0.5% lidocaine without preservative is injected. Anesthesia is expected in 3 to 5 minutes. Bupivacaine should not be selected for this technique because of the severe cardiovascular complications associated with its use.[32]

Most procedures performed under these techniques have lasted less than 15 minutes, and tourniquet pain was not encountered. Tourniquet pain may be eliminated by inflating the distal tourniquet, which should be in an anesthetic area, then deflating the proximal tourniquet. Staged cuff deflation is recommended following procedures lasting less than 30 minutes.

SURFACE ANESTHESIA

Skin

A topical anesthetic agent can be of great value in performing painful peripheral procedures in children. Many attempts have been made to compound a formulation of local anesthetics that will produce effective anesthesia when applied topically to intact skin. Mixed in equal amounts, the solid pure bases of lidocaine and prilocaine constitute an eutectic mixture of local anesthetics (EMLA) that forms an oil at temperatures greater than 16°C. This mixture has been tested in Europe on adults and premedicated children and in the United States on unpremedicated pediatric outpatients to produce skin analgesia before venipuncture.[23]

To be fully effective, an EMLA requires very careful application. After an appropriate amount (2.5 g) is applied over a preselected vein, an occlusive dressing must be applied and left undisturbed for 60 minutes.

Although EMLA does alleviate the physical pain associated with venipuncture, it does not address the emotional component of anticipated pain that children associate with venipuncture. In a recent study, EMLA was no more effective in this regard than the standard intradermal injection of lidocaine.[23] The ultimate place of EMLA in pediatric ambulatory anesthesia remains to be established.

Mucous Membranes

Topical anesthesia may be applied to the nose and nasopharynx before passage of a nasotracheal tube to reduce response to an oral airway in the pharynx or before passage of an endotracheal tube.

Topical anesthesia is a great help during diagnostic or operative bronchoscopy. The dose of lidocaine for topical spray on the trachea should not exceed 2 mg/kg. If the calculated volume of the 4% solution is too small, a more dilute formulation should be selected. Topical anesthesia also may be useful in cystoscopic procedures. An aqueous jelly applied to the urethra often enables one to use very light supplemental general anesthesia. Topical anesthesia also may be used for the removal of foreign bodies from the eyes (0.5% proparacaine) and shrinkage of the nasal turbinates (4% cocaine).

LOCAL INFILTRATION

Whether employed by surgeon or anesthesiologist, local infiltration anesthesia probably has a greater potential in pediatric ambulatory anesthesia than is currently appreciated. In addition to its usefulness for suturing lacerations and for other minor procedures, local anesthesia may be the best technique for performing superficial procedures on older children. Two agents have been used primarily for infiltration anesthesia; each seems equally effective. A total of 10 mg/kg of 0.5% or 1.0% procaine or a total of 5 mg/kg of 0.25% lidocaine is within the margin of safety.

The addition of epinephrine, which has a vasoconstrictive effect, would increase the permissible amount of anesthetic. However, unless the solutions were limited to a strength of 1:400,000, one would run the risk of exceeding the safe dosage range for this agent. Consequently, epinephrine is not used at Children's National Medical Center when the injection is performed purely for analgesia. If the epinephrine is infiltrated for the purpose of reducing bleeding, as in plastic surgery, the total allowable dose is considered to be 10 μg/kg if the child is receiving halothane and is not hypercarbic.

SUMMARY

Regional anesthesia is an accepted approach to postoperative analgesia in children. The anesthesiologist has a wide choice of agents and techniques that can be tailored to the needs of the individual patient. For inguinal herniorrhaphy or orchiopexy, a caudal, ilioinguinal and iliohypogastric, or instillation block can be used. For circumcision or hypospadias surgery, one may choose a caudal block; alternatively, a dorsal nerve block, ring block, or topical lidocaine may be used at the conclusion of surgery. Spinal anesthesia is a viable alternative to general anesthesia in high-risk neonates undergoing surgery below the diaphragm. Intravenous regional, local infiltration, and topical analgesia are as effective in children as they are in adults and should not be forgotten.

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Body Temperature and Anesthesia

*Bruno Bissonnette, MD, FRCPC**

Homeothermic species (e.g., mammals and birds) require a nearly constant internal body temperature. When internal temperature deviates significantly from normal, metabolic function usually deteriorates and death may result. It was not until 1714 that Gabriel Fahrenheit provided a standard temperature scale allowing comparisons of absolute temperature changes. Temperature monitoring during surgery is now routine because perianesthetic thermal perturbations are common. Under normal conditions, the human thermoregulatory system controls central body temperature within 0.4°C of normal, at ≈37°C. Hypothermia is a common result of either cold exposure alone or exposure combined with drugs or illness that decrease thermoregulatory efficacy. During anesthesia and surgery, hypothermia is common due to anesthetic-induced inhibition of thermoregulatory mechanisms and patient exposure to a cold operating room environment. An understanding of normal and anesthetic-influenced thermoregulation perturbations will facilitate prevention and management of these complications.

This article (1) reviews normal thermoregulatory mechanisms and quantitative techniques of evaluating regulatory responses to thermal perturbations; (2) discusses how anesthesia causes hypothermia by inhibiting normal thermoregulatory responses; and (3) evaluates different strategies for preventing and treating perioperative hypothermia.

NORMAL THERMOREGULATION

Thermoregulation is similar to many other physiologic control systems in that the brain uses negative feedback to minimize perturbations from normal values.[79] Several models describe the thermoregulatory system and predict responses to thermal perturbations under various conditions.[11, 70, 82] Although these models differ in complexity and type (e.g., mechanical versus electrical), none actually describes how animals regulate temperature. (The actual mechanisms controlling temperature are not well understood.) However, they provide a useful framework for the understanding of mammalian defenses against thermal stress. Temperature is centrally regulated, principally by the hypothalamus, but is based on signals derived from nearly every type of tissue including other parts of the brain, spinal cord, deep central tissues, and the skin surface (Fig. 1). The processing of thermoregu-

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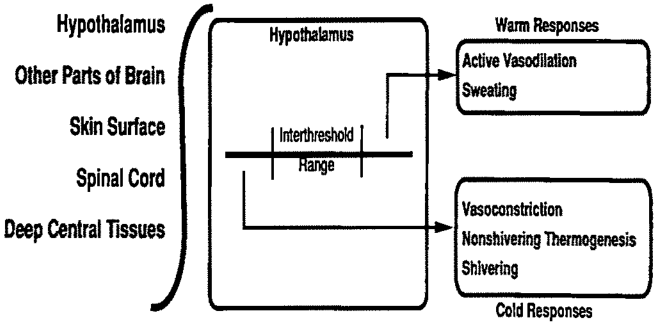

Figure 1. Thermoregulatory control mechanisms. Mean body temperature is the integrated thermal input from a variety of tissues including the brain, skin surface, spinal cord, and deep central structures. Mean body temperature below the thesholds for response to cold provokes vasoconstriction, nonshivering thermogenesis, and shivering. Mean body temperature exceeding the hyperthermic thresholds produces active vasodilation and sweating. No thermoregulatory responses are initiated when mean body temperature is between these thresholds (the "interthreshold range"). (Adapted from Sessler DI: Temperature monitoring. *In* Miller RD (ed): Anesthesia, ed 3. New York, Churchill Livingstone, 1990, p 1228; with permission.)

latory information occurs in three phases: afferent thermal sensing, central regulation, and efferent response.

Afferent Thermal Sensing

Temperature information is obtained from thermally sensitive cells throughout the body. For instance, ambient temperature is detected peripherally by anatomically distinct warm and cold receptors. Cold-sensitive cells travel to the hypothalamus and other central structure through A-delta fibers, whereas warm input traverses unmyelinated C fibers. Warm receptors adapt their firing rate when the temperature increases and cold receptors when the temperature decreases. The C fibers also detect and convey pain sensation, which is why intense heat cannot be distinguished from sharp pain.[64, 65] Most ascending thermal information traverses the spinothalamic tracts in the anterior spinal cord, but no single spinal tract is critical for conveying thermal information.[33]

Central Regulation

The hypothalamus regulates temperature by comparing integrated thermal inputs from the skin surface, neuroaxis, and deep tissues with *threshold* temperatures for heat and cold (Fig. 1). However, structures in the brainstem and the spinal cord also possess some thermoregulatory capabilities. The extent to which and how these "lower" structures contribute to overall regulation is unknown. When the integrated input of all sources exceeds one of the thresholds, responses are initiated to maintain adequate body temperature. The slope of response intensity versus the difference between thermal input and the threshold temperature is the *gain* of that response (Fig. 2). The difference between the lowest warm and highest cold thresholds indicates the thermal sensitivity of the system. The *interthreshold range* (temperature range over which no regulatory responses occur) is typically ≈0.2°C. Thus, while the brain presumably detects temperature changes within this range, changes do not trigger regulatory responses until they reach one of the thresholds. How the body determines absolute threshold temperatures is unknown, but the thresholds appear to be influenced by many factors such as circadian

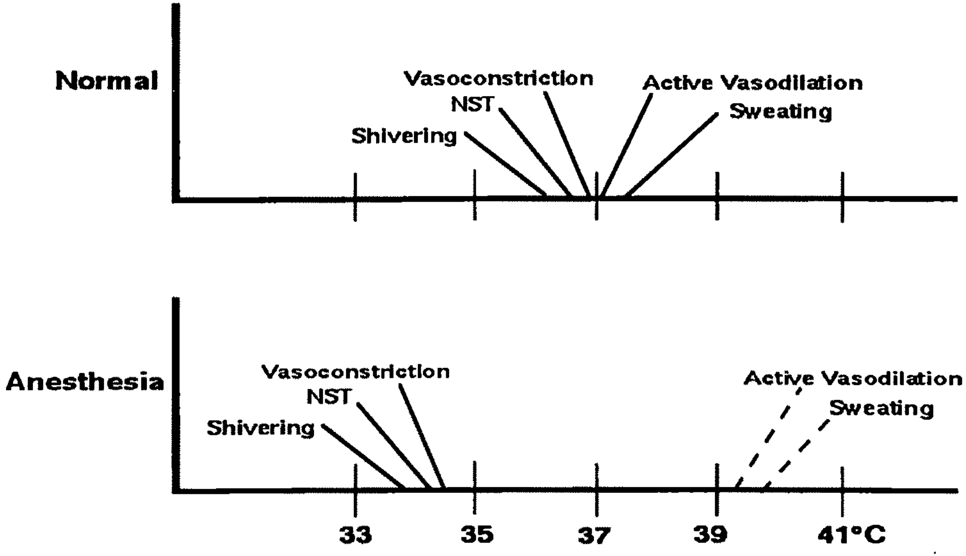

Figure 2. Thresholds and gains for common thermoregulatory responses in awake and anesthetized humans. Vertical lines represent different effector responses and dark horizontal lines show mean body temperature. The intersection of each line with the temperature scale is the threshold, and the slope indicates the gain of that response. Thermoregulatory sensitivity is shown as the distance between the first cold response (vasoconstriction) and the first warm response (active vasodilation); temperatures within this range will not elicit thermoregulatory compensation. Thresholds in unanesthetized individuals are closer than illustrated (i.e., ≈0.2°C), and the gains of responses are higher. During general anesthesia (bottom), shivering is not shown because it is inhibited by muscle relaxants and local effects of inhaled anesthetics. The thresholds for cutaneous vasoconstriction and nonshivering thermogensis responses are shifted down to ≈35.0°C in newborns and infants,[8] and it seems to be ≈34.5°C in children and adults.[8, 72] In both cases it is influenced by the anesthetic type and dose. The effects of anesthetics on active vasodilation and sweating are unknown. (*Modified from* Sessler DI: Temperature monitoring. *In* Miller RD (ed): Anesthesia, ed 3. New York, Churchill Livingstone, 1990, p 1229; with permission.)

rhythm, exercise, food intake, infection, thyroid gland perturbations, anesthetics and other drugs (including alcohol, sedatives, and nicotine), and cold and warm adaptation. Central regulation is intact from infancy, but may be impaired in elderly or extremely ill patients. We now know that regulatory responses are based on mean body temperature, i.e., based on integrated thermal signals from nearly every tissue in the body, not simply central temperature.

Mean body temperature is a physiologically weighted average reflecting the thermoregulatory importance of various tissues. In unanesthetized subjects, mean body temperature is $\approx 0.85\ t_{central} + 0.15\ t_{skin}$, where average skin temperature can be determined using the formula $t_{skin} = 0.3\ (t_{chest} + t_{arm}) + 0.2\ (t_{thigh} + t_{leg})$.[66, 80] The system is further complicated by the observation that different responses integrate thermal inputs in different ways (e.g., behavorial responses in humans are determined almost entirely by skin-surface temperature, not by tissue heat content, cutaneous heat flux, or central temperature.[27, 75] The most commonly described thermoregulatory model is a setpoint system in which hypothalamic temperatures above or below a predetermined level trigger warm or cold defenses, respectively. More useful is a model in which a system of thresholds and gains predicts thermoregulatory responses. The threshold for a particular response is the temperature at which that response is triggered. The actual mechanism used by the brain to set and recognize threshold temperatures remains unknown. The intensity of the response (e.g., degree of vasoconstriction, sweating rate) is the gain of the system (see Fig. 2). It is usually expressed as the slope of an intensity plot versus ΔT, where ΔT is the difference between integrated body temperature and the thermoregulatory threshold. Each response has its own threshold and gain. The thresholds for warm defenses are higher than those that prevent hypothermia. Temperatures that fall between the highest cold response and the lowest warm defense form the interthreshold range. The mean body temperatures within this interthreshold range do not trigger thermal responses (see Fig. 1). However, this interthreshold "neutral" range can be affected by a number of factors, such as anesthesia. It is likely that some thermoregulatory responses can be directed from the spinal cord, which would explain why vasoconstriction and vasodilation responses are activated before metabolically costly responses (e.g., shivering) (see Fig. 2).

Efferent Responses

The body responds to thermal perturbations differing from the threshold by responses that increase metabolic heat production (nonshivering thermogenesis and shivering), decrease environmental heat loss (active vasoconstriction and behavorial maneuvers), or increase heat loss (active vasodilation and sweating) (Table 1).

Behavorial responses to environmental temperatures outside the thermoneutral range (≈28°C for undressed adult humans) are quantitatively, the most important thermoregulatory effectors in humans (e.g., heating a home, putting on a sweater).

Cutaneous vasoconstriction is the most consistent and first thermoregulatory

Table 1. *Thermoregulatory Response Mechanisms Occurring in Humans*

COLD	WARM
Behavioral	Behavioral
Vasoconstriction	Vasodilation
Nonshivering thermogenesis	Sweating
Shivering	

Modified from Sessler DI: Temperature monitoring. *In* Miller RD (ed): Anesthesia, ed 3. New York, Churchill Livingstone, 1990; with permission.

response to hypothermia. Total digital skin blood flow is divided into nutritional (capillary) and thermoregulatory (arteriovenous shunts). Thermoregulatory decreases in cutaneous blood flow are greatest (up to 100-fold) in arteriovenous shunts of the hands, feet, ears, lips, nose, etc.[29, 37] Shunts are typically 100 μm in diameter, which means that one can convey 10,000-fold as much blood as a comparable length of 10-μm diameter capillary.[30] Shunt flow is primarily mediated by norepinephrine (released by presynaptic adrenergic terminals), which binds alpha$_2$ receptors that are sensitized by local cooling and inhibited by temperatures greater than or equal to 35°C.[72] However, flow also decreases in the more numerous capillaries.[19] Despite impressive decreases in cutaneous perfusion resulting from thermoregulatory vasoconstriction, heat loss from the whole body is minimal (i.e., 25%).[78] Losses from the hands and feet decrease ≈50%, but only ≈17% from the trunk.

Active vasodilation in response to warm stress is not simply the absence of active vasoconstriction and can be quite effective in dissipating heat.[23, 69]

Nonshivering thermogenesis is an increase in metabolic heat production without increases in mechanical muscular work. Skeletal muscle and brown fat tissue are the major sources of nonshivering heat. It is measured as an increase in oxygen consumption in the absence of physical activity (including shivering). Heat production is activated primarily by beta-sympathetic innervation, which uncouples oxidative phosphorylation in the mitochondria of specialized fat cells (brown adipose tissue) and in skeletal muscle.[1, 41] Nonshivering thermogenesis is most prominent in physically small species and the young of most species.[22]

Shivering is thought to occur only when maximal vasoconstriction, nonshivering thermogenesis, and behavioral maneuvers are insufficient to maintain an appropriate mean body temperature.[34, 35] Vigorous shivering can briefly increase metabolic heat production four-fold, but will sustain only twofold increases. It is characterized by a high-frequency, irregular muscular activity that first appears in upper body muscles. Typically, tremor spasms wrack the body, producing a "waxing-and-waning" electromyographic pattern.[89]

Sweating increases evaporative cutaneous loss during periods of heat stress. Because heat of vaporization of water is high, sweating is remarkably effective: it can increase heat loss to the environment fivefold, making it proportionately more effective than the combined defenses against cold.[26]

Efferent mechanisms in infants are less effective than in adults. Nonshivering thermogenesis is their primary response to hypothermia, but it compensates poorly for ineffective shiver and limited vasoconstriction. Infants who are premature or small for gestational age have an inordinately large skin-surface area compared with their body mass. Therefore, they lose proportionately more metabolic heat through skin than adults in a similar environment.[15] The combination of increased heat loss, diminished ability to produce endogenous heat, and finally a diminished thermoregulatory response efficacy makes infants prone to hypothermia.

The range of tolerable thermal environments is determined mainly by the efficacy of the thermoregulatory mechanisms. Extremes of age, infirmity, or drug usage will provoke thermal disturbances despite normal ambient temperatures that can result in inadequate responses that physically fit individuals would otherwise tolerate easily.

TEMPERATURE MONITORING

Temperature is a measure of an object's internal kinetic and potential energy (tendency to lose heat to another object at a different temperature). Temperature is usually expressed in degrees centigrade using the scale developed by Celsius in 1742.

Heat, in contrast, is the energy that can be transferred to another object at a different temperature. Heat is expressed in calories (amount of heat energy required to raise the temperature of 1 g of water 1°C). One calorie equals 4.2 J. Specific heat capacity is the number of joules required to raise 1 kg of a substance by 1°C; its units are $J \cdot kg^{-1} {}^{\circ}C^{-1}$.[40]

Indications for Temperature Monitoring

Perioperative measurements of body temperature help detect hypothermia and malignant hyperthermia. Central temperature monitoring is now considered the "standard of practice" during general anesthesia. While malignant hyperthermia is (justifiably) the most threatening thermal complication, hypothermia is the most common (see the section on Perioperative Hypothermia). Mild hypothermia (34°C–35.5°C) may occur during a prolonged anesthetic procedure, which justifies monitoring body temperature. Central temperature should always be monitored in anesthetized infants and children because they can show rapid and profound hypothermia.

Thermometers

Recorded temperatures may deviate from "true" temperature because (1) the thermometer is imprecise (i.e., thermometer reading may differ from the probe temperature); (2) the temperature of the probe differs from that of the surrounding tissue (i.e., and artifactual reading); or (3) the temperature of the probe (in a convenient location) differs from the temperature of interest (in a poorly accessible tissue such as the brain).[6] However, virtually all clinically used thermometers provide temperature readings with an absolute accuracy near 0.1°C; the major difficulty is choosing a suitable site to measure. There are many different thermometers available, such as mercury in glass, thermistors, thermocouples, infrared thermometers, temperature-sensitive liquid crystals, etc. Thermocouples (which measure a temperature-dependent bimetal electrical potential) are by far the most frequently used. They are sufficiently inexpensive, offer a single use, and are available in a wide range of skin configurations, including those designed for tympanic membrane, pulmonary artery, esophageal, and rectal measurements. Temperature-sensitive liquid crystals can be incorporated into a plastic backing and used for skin-surface thermometry. Although easy and convenient to use in pediatric anesthesia and relatively inexpensive, these devices generally do not have the range or accuracy necessary for clinical use.[50]

Temperature Monitoring Sites

Temperatures monitored from various sites have been considered valid when they compared favorably with tympanic membrane (i.e., hypothalamic) temperature.[20] However, there is little physiologic support for an exclusive reliance on hypothalamic temperature since it is now known that integrated input from the entire body determines thermoregulatory responses. Evidence in animals and birds indicates that multiple, redundant thermal inputs from nearly every part of the body are integrated by both the spinal cord and hypothalamus.[82, 83] It is likely that thermal sensing is similar in humans. Thus, the most useful approach to temperature monitoring is to recognize that temperatures of different tissues are "real," but that the physiologic and practical significance of each varies. In unanesthetized humans, tympanic membrane, pulmonary artery, rectal, nasopharyngeal, and esophageal temperatures usually are similar, so that any one reflects most of the noncutaneous input to the thermoregulatory system.[20] Oral temperature is less reliable.[91] Esophageal, rectal, and axillary temperatures recorded in infants and children given halothane/nitrous oxide anesthesia for noncardiac surgery rarely differed from tympanic membrane temperature by more than 0.2°C (Fig. 3).[6]

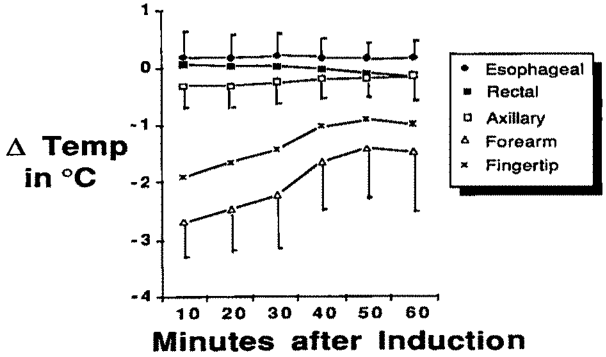

Figure 3. The average difference between temperatures at five different measurement sites and tympanic membrane temperature in 20 children weighing 5 to 30 kg. A difference of ≈0.2°C between central sites and axilla was recorded. This difference is small compared with the physiologic differences between individuals and indicates that any one reflects the bulk of central thermoregulatory input. (*From* Bissonnette B, et al: Intraoperative temperature monitoring sites in infants and children and the effect of inspired gas warming on esophageal temperature. Anesth Analg 69:192–196, 1989; with permission.)

Axillary temperatures correlated well with central temperatures in these children, although they did not in a previous study in adults.[20] An important difference in infants and children is that the thermometer probe can be carefully placed over the artery and is not insulated from fat, as in adults.[6] Temperature probes are frequently incorporated into disposable esophageal stethoscopes; this system will only reliably measure central temperature when the probe is placed in the distal third of the esophagus (at the point at which maximum heart tones are heard).[45, 90] Even properly placed esophageal probes are slightly influenced in children and infants by respiratory gas temperatures in the nearby trachea.[6]

Skin surface temperatures do not correlate well with central temperatures and not only are skin-surface temperatures significantly lower than central temperatures, but the difference between skin and central temperatures does not remain constant.[6, 48] Thus, simply adding a constant value (e.g., 2.2°C) to an arbitrary skin temperature, such as the forehead, is unlikely to provide adequate indication of central temperature.[12, 44] Because skin-surface temperatures do not correlate well with central temperatures, they should not be considered a substitute for tympanic membrane, nasopharyngeal, or esophageal temperature. Furthermore, the correlation between skin and central temperatures is likely to be especially poor during an episode of malignant hyperthermia (because circulating catecholamine concentrations increase 20-fold, markedly reducing cutaneous perfusion).

PERIOPERATIVE HYPOTHERMIA

General Principles

A dramatic decrease in infant mortality from 98% to 23% was reported when rectal temperature below 32°C was compared with normal rectal temperature.[32] General anesthesia decreases the temperature threshold at which the body initiates thermoregulation. Mild intraoperative hypothermia 1°C–3°C below normal is common and results from (1) an ≈30% decrease in metabolic heat production during anesthesia[86]; (2) increased environmental exposure; (3) anesthetic-induced central thermoregulatory inhibition[72, 76]; and (4) redistribution of heat within the body.[39a]

Causes of Perioperative Hypothermia

Hypothermia has a typical pattern during general anesthesia and usually develops in three phases. Initially, central temperature decreases rapidly during the first hour postinduction of anesthesia (initial hypothermia) when peripheral vasodilation redistribute heat within the body. Heat loss to the ambient environment leads to an approximately linear decrease in mean body temperature (typically 0.5°C–1.0°C/h, lasting 2–3 hours). In the final phase, a thermal steady state (metabolic heat production equals environmental heat loss) is achieved during which central temperature remains constant.[21, 68] However, it has been shown in infants and children that the third phase (plateau) reported in adults does not exist but rather a rewarming phase takes place.[8]

Anesthesia decreases heat production because postural and respiratory (during mechanical ventilation) muscular activity ceases, and metabolic rate in other tissues, especially the brain, decreases.[87, 93] Conduction, convection, radiation, and evaporation contribute to environmental heat loss during anesthesia and surgery.

Conductive heat losses are equal to the temperature difference between the skin and the adjacent environmental surface with which the individual makes direct contact. Relatively little heat is lost during surgery via conduction to the environment because patients are well insulated from surrounding objects. However, the energy needed to warm irrigation solutions and intravenous fluids can significantly reduce body temperature.

Convective losses increase in proportion to the temperature difference between the body surface and the square root of air velocity surrounding the patient. (Convective losses are experienced on a daily basis as the "wind chill factor.")

Radiation increases by the fourth power of the temperature difference between two objects (in this case, skin and the walls of the operating room). It is independent of atmospheric conditions in a manner similar to light passing through a vacuum. An infant in an operating room will warm up walls and solid objects by exchanging radiant energy. At 22°C, 70% of total heat loss is via radiation.[31] Both convective and radiative losses are dramatically reduced by even a single covering layer. Thus, a thin shirt (providing negligible insulation) considerably increases thermal comfort.

Evaporative losses involve several components: (1) sweating, (2) insensible water loss from the skin and the respiratory tract, and (3) evaporation of liquids applied to the skin such as antibacterial solutions. Evaporative losses from the skin surface are negligible except during sweating. Newborn infants will sweat in an effort to prevent overheating only when environmental temperature exceeds 35°C and rectal temperature is above 37°C.[32] Rectal temperature must rise above normal before the newborn sweats.[36] Infants of less than 30 weeks gestation appear to have immature sweat glands, resulting in defective sweat mechanisms.[32]

A small amount of heat is lost when dry inspired respiratory gases are humidified by water evaporating from tracheobronchial epithelium. In adults, respiratory losses account for only 5% to 10% of total heat loss during anesthesia and surgery.[4] Insensible water loss accounts for approximately 25% of the total heat dissipated. Because minute ventilation on a per kilogram basis is higher in children and infants than in adults, respiratory losses represent about one third of this total heat loss.[18, 55] Heat loss from the respiratory tract increases if the infant breathes cool dry gas.[5, 7]

Hypothermia is more likely to occur if the infant is wet or in contact with wet drapes because of increased evaporative heat loss. Finally, heat lost from evaporation inside large surgical incisions may equal all other sources of intraoperative loss.[67]

Thermoregulation During Anesthesia

General anesthesia decreases the thermoregulatory threshold temperatures triggering responses to hypothermia by ≈2.5°C, and probably increases the threshold temperatures initiating reponses to hyperthermia by a comparable amount (see

Fig. 2).[74] Anesthesia-induced widening of the interthreshold range produces a broad temperature range over which active thermoregulatory responses are absent. Within this range, patients are poikilothermic, and body temperature changes passively in proportion to the difference between metabolic heat production and heat loss to the environment. Vasoconstriction and nonshivering thermogenesis are the only thermoregulatory responses available to anesthetized, paralyzed, hypothermic patients. Patients who become sufficiently hypothermic during surgery (e.g., central body temperatures ≈34.5°C) demonstrate a profound peripheral cutaneous vasoconstriction.[72, 74, 90] The temperature at which vasoconstriction and nonshivering thermogenesis occurs identifies the thermoregulatory threshold for the anesthetic agent and dose or concentration administered. The thermoregulatory threshold in healthy, adult patients given halothane–oxygen[72] or nitrous oxide–fentanyl[74] anesthesia for elective, donor nephrectomy is ≈34.5°C. The potent vasodilatory effect of isoflurane has been shown in a similar patient. Its effect on the thermoregulatory threshold is inversely proportional to the inhaled concentration, and it is equal to ≈3°C percent end-tidal concentration.[90] The vasoconstriction threshold in infants and children anesthetized with isoflurane differs little from that in adults (Fig. 4).[8] Thus, the percentage increase in regulatory thermogenesis is similar in infants and adult humans. The high surface area to mass ratio in infants, which allows relatively rapid loss of heat to the environment, is largely offset by an intrinsically high metabolic rate. Environmental heat loss is further minimized by well-developed thermoregulatory vasoconstriction.[8]

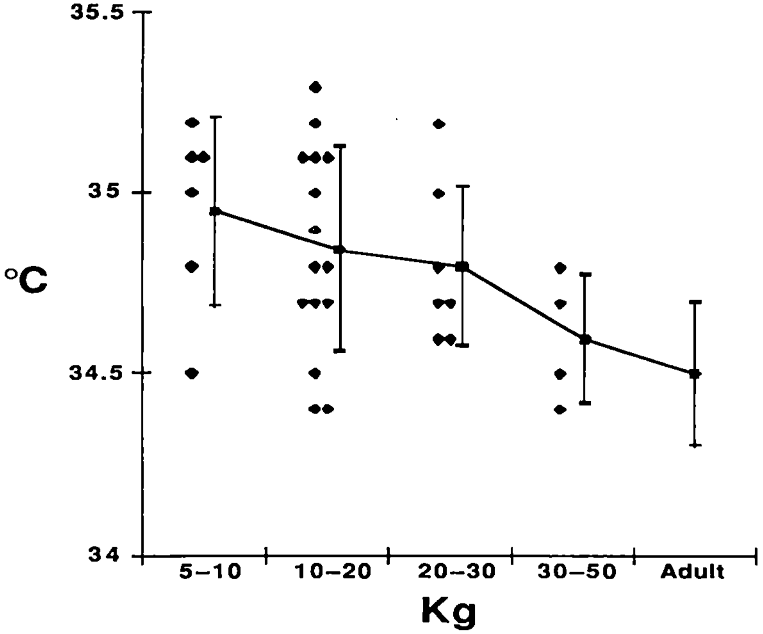

Figure 4. The thermoregulatory thresholds (tympanic temperature at which the laser Doppler perfusion index decreased to 50% of control) in 33 healthy children and infants undergoing abdominal surgery with isoflurane (≈0.75%) and oxygen. The threshold in the adults was estimated using the mean age-corrected isoflurane concentrations given to the children and infants. There is little difference in the threshold temperatures as a function of age. (*From* Bissonnette B, Sessler DI: The thermoregulatory threshold in infants and children with isoflurane and caudal bupivacaine. Anesthesiology 73:1114–1118, 1990; with permission.)

Although there is a trend toward decreased inhibition in smaller infants and children given similar isoflurane concentrations, differences between the groups were not statistically significant and spanned only ≈0.3°C. It indicates that inhibition of thermoregulatory vasoconstriction is similar in anesthetized infants and children and relatively independent of body weight.[8] Relatively constant thermoregulatory inhibition in infants and children of different ages is in marked contrast to the minimum alveolar concentration of isoflurane, which increases to ≈150% of the adult requirement in infants 1 to 6 months of age. Thus, inhibition of thermoregulatory vasoconstriction in infants and children is greater than in adults when administered anesthetic concentrations are adjusted for age.[8] The threshold in adults given nitrous oxide–fentanyl anesthesia is similar (34.4°C ± 0.5°C).[74] However, the influence of narcotics on thermoregulation remains controversial because their effects in animals differ from those in humans. Nitrous oxide inhibits behavioral thermoregulation in mice.[39] Ketamine, in anesthetized adults, appears to cause less thermoregulatory suppression than other anesthetics.[39] Threshold temperature during rewarming on cardiopulmonary bypass is difficult to evaluate because of large thermal gradients within the body.[51]

A notable feature of intraoperative thermoregulatory studies is that central temperatures rarely continue to decrease once thermoregulatory vasoconstriction is triggered.[72, 74, 96] These data are consistent with the clinical observation that central temperatures below ≈34.5°C (typical thermoregulatory threshold) are unusual in surgical patients who not deliberately cooled. Thermal steady state (in the absence of heat redistribution within the body, which is unlikely after 2 to 3 hours of surgery) requires that metabolic heat production equals environmental heat loss. Therefore, patients must increase heat production and/or decrease heat loss to prevent further hypothermia. Heat loss from patients to the environment is a function of the difference between skin surface and ambient temperatures. Loss, therefore, decreases passively (i.e., without regulatory intervention) as patients become increasingly hypothermic. Thermoregulatory vasoconstriction also actively decreases heat loss, but only by 10% to 15%, which is consistent with the relatively small effect of vasoconstriction in unanesthetized humans. The extent to which nonshivering thermogenesis is important in anesthetized adults remains unclear. However, oxygen consumption appears to increase only slightly when patients are vasoconstricted.[73] In contrast, thermoregulatory vasoconstriction in infants anesthetized with halothane is associated with a large increase in metabolic rate (Bissonnette B, Sessler DI: Unpublished data) (Fig. 5).

A simultaneous increase in oxygen consumption, carbon dioxide production, and systemic noradrenaline has been observed in infants anesthetized with isoflurane and paralyzed with vecuronium and is consistent with the increased role of nonshivering thermogenesis in unanesthetized infants (Bissonnette B, Sessler DI: Unpublished data). Infants differ from adults in that intraoperative thermoregulatory responses are sufficiently effective to significantly increase central temperature despite constant ambient temperatures.

Benefits and Risks of Mild Hypothermia

Temperatures only 2°C to 3°C below normal confer significant protection from focal cerebral ischemia[14, 43, 49] and systemic hypoxia.[46, 47] Inadequate tissue oxygen supply forces cells to use anaerobic metabolism which is both inefficient and unlikely to provide adequate energy. Since hypothermia reduces the metabolic rate in all cells, it generally provides greater protection against ischemia and hypoxia than drugs such as barbiturates, which selectively reduce metabolic rate only in neurons. The lower metabolic rate decreases cellular energy needs and toxic waste production by anaerobic metabolism. However, the value of mild intraoperative hypothermia has yet to be demonstrated clinically and may be harmful in pediatric patients.

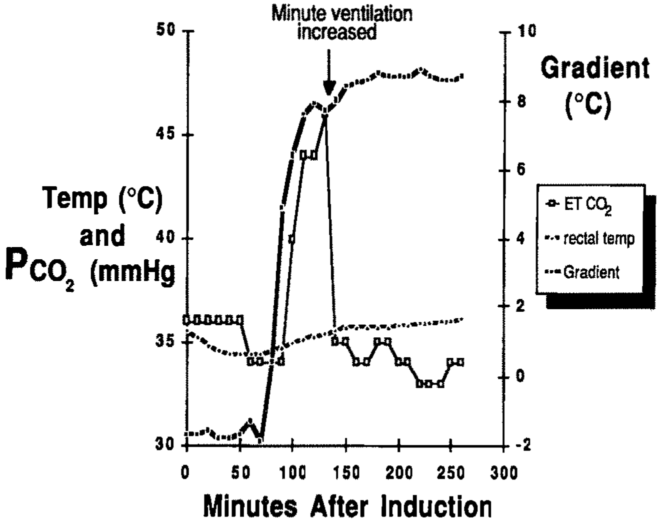

Figure 5. Typical thermoregulatory vasoconstriction and nonshivering thermogenesis in an 8.4-kg infant anesthetized with halothane and oxygen during abdominal surgery. The skin-temperature gradient (an index of peripheral vasoconstriction) increased ≈10°C when the thermoregulatory threshold was reached, at a central temperature of 34.5°C. End-tidal CO_2 simultaneously increased from 34 to 47 mm Hg (with constant ventilation), reflecting a significant increase in CO_2 production (and presumably, oxygen consumption). Minute ventilation was increased when the partial pressure of CO_2 reached 47 mm Hg.

The most common complication of perioperative hypothermia is a shivering-like tremor observed during recovery from general anesthesia in ≈40% of patients.[18, 55] The tremor can double metabolic rate[40] and may cause hypoxia and hypercarbia in patients with preexisting pulmonary disease.[65] Although, hypothermia is believed to produce respiratory depression especially in infants, there is little evidence that mild postoperative reductions in body temperature cause clinically significant problems. Prolonged duration of recovery from general anesthesia has also been attributed to perioperative hypothermia. However, a number of studies suggest that recovery is rapid in both infants and adult patients.[5, 7]

Prevention and Treatment of Hypothermia

Intraoperative hypothermia can be minimized by any technique that limits heat loss to the environment due to cold operating rooms, surgical incision, dry and cold breathing gases, and cold intravenous fluids. The basal metabolic rate in adult humans is ≈80 W (which is reduced ≈30% during general anesthesia),[89] and the specific heat of humans is ≈0.83 $kcal \cdot kg^{-1} \cdot C^{-1}$.[13] Since respiratory losses account for only 5 to 10 W,[2] cutaneous losses are the primary determinant of heat balance. Consequently, operating room temperature is the most critical factor determining heat loss during surgery. At room temperatures greater than or equal to 21°C, most adult patients remain normothermic.[59-61] It is suggested that for premature newborns and infants, the operating room may require ambient temperatures near 26°C.[3]

The initial 0.5°C decrease in core temperature that occurs immediately after induction of anesthesia is difficult to prevent since it is caused by central redistribution of cooled blood from the vasodilated peripheral circulation. However, to limit further decrease in body temperature resulting from redistribution of heat within the body, skin-surface warming before induction of anesthesia should be provided. It should be noted that aggressive warming causes skin-surface vasodilation and increases temperature of the peripheral compartment to values approaching those of central tissues. The net result may be an increase in mean body temperature (paradoxically, central temperature actually decreases slightly due to peripheral loss). Further vasodilation on induction of anesthesia promotes additional mixing between the central and peripheral compartments, but since their temperatures are similar, central hypothermia is avoided.

Heat loss due to tracheobronchial warming and humidification of respiratory gases can be minimized by adding an active airway heater/humidifier or passive heat- and moisture-exchanging filters ("artificial noses") to the anesthesia circuit.[17, 63, 90] Differences in efficiencies among heat- and moisture-exchanging filters are small.[10] Altough airway humidification contributes only slightly to maintaining normothermia in adults, considerable evidence suggests that a relative humidity of at least 50% maintains normal ciliary function in the trachea and helps prevent bronchospasm.[16, 53, 54] Humidification to this level (easily provided by heat- and moisture-exchanging filters) is probably appropriate during prolonged procedures to maintain ciliary functions. In infants and children artificial noses are almost as effective as active humidifier systems[5, 7] and are easier to use and less likely to produce complications, including respiratory burns, breathing circuit disconnection, and overhumidification.[55, 64, 83, 86–87] Because minute ventilation is higher (on a per kilogram basis) in infants than adults, airway humidification is more effective than has been observed in adults.[5, 7, 25, 31] Even artificial noses with a dead space ≈1 mL produce trivial airway resistance and can be used safely with the smallest infants.[62]

Heat loss due to cold intravenous fluids becomes significant when large amounts of crystalloid solution or blood are administered. Fluid warmers minimize these losses and should be used when large amounts of intravenous fluids are required or when blood is administered.[62] A variety of passive and active skin-surface warmers is available, including circulating hot water blankets[29, 58, 88] and infrared radiant heaters.[9, 43, 45] However, the best method of preventing and treating intraoperative and postoperative hypothermia is a recently developed convective warmer. It uses warm air forced through a disposable blanket to raise the effective ambient temperature around patients to ≈43°C.[80]

During short surgical operations (e.g., ophthalmic procedures) thermal steady state will be achieved very rapidly. Therefore, no additional warming is needed. Even heat loss greater than metabolic production will have no effect during short procedures because the decrease in core temperature will be negligible. Hypothermia is most often associated with prolonged and extensive operations, and judgment should be used to decide when warming technique may be required to maintain normothermia.

SUMMARY

Thermoregulatory responses involve afferent thermal sensing, central regulation and efferent responses. Central responses are based on thermal signals from nearly all body tissues and are integrated in the hypothalamus. Some thermoregulatory control seems to be mediated from the spinal cord and the brainstem. The efferent responses (behavorial, cutaneous vasoconstriction or vasodilation, nonshivering thermogenesis, shivering, and sweating) may interpret and respond differently to afferent input. Therefore, there is no evidence that body temperature is controlled with a unique temperature setpoint that determines regulatory responses to thermal perturbations. Body temperatures can be measured using a variety of thermometers. Most clinically used thermometers are intrinsically accurate; the difficulty is in choosing appropriate sites to make temperature measurements. However, pediatric patients offer more accuracy and liberty in regard to temperature monitoring sites. In infants and children not deliberately cooled, temperatures of the central sites (tympanic membrane, nasopharynx, esophagus, axilla, and rectum) are similar. Temperature measurement in any one, thus, represents a reasonable approximation of central body temperature. Skin-surface temperature monitoring should be used with caution since mean body temperature can change considerably without any alteration in central temperature.

Perioperative hypothermia results from decreased metabolic heat production, increased environmental heat loss, redistribution of heat within the body, and anesthetic-induced inhibition of thermoregulation. The initial rapid decrease in core temperature innediately following induction of general anesthesia seems to be related largely to redistribution of heat within the body (this does not change mean body temperature). An imbalance between metabolic heat production and heat loss caused by convection and radiation from the skin surface and evaporation from tissues exposed by surgical incisions are the most important contributors to intraoperative hypothermia.

After several hours of surgery and anesthesia, thermal steady state develops when metabolic heat production equals heat loss to the environment. Steady state can be passive or result from active thermoregulatory vasoconstriction and nonshivering thermogenesis. The central temperature at which thermoregulatory threshold triggers peripheral cutaneous vasoconstriction is similar for all ages (34.5°C–35.0°C) during halothane or nitrous oxide-fentanyl anesthesia. Nonshivering thermogenesis appears to significantly increase metabolic heat production in infants. Despite their large surface to body mass ratio, they show a strong cutaneous vasoconstrictive response and introperative rewarming.

Perioperative hypothermia can be prevented and treated by heating intravenous fluids, airway humidification, and skin surface warming. Cutaneous warming is considerably more effective than airway humidification and is the only way to ensure normothermia.

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Blood, Colloid, and Crystalloid Therapy

*Charles J. Coté, MD**

Perhaps nothing in pediatric anesthesia has undergone a more radical change in recent years than the management of blood products, fluid replacement strategies, and fasting before anesthesia. This chapter discusses advances in each of these areas.

INTRAVENOUS FLUID THERAPY STRATEGIES

Crystalloid

The administration of intraoperative crystalloid therapy is designed to replace deficits as a result of fasting, maintenance fluids (evaporative and urinary losses), and third space losses (loss of fluid from the extravascular space as in edema formation). Therefore, whenever approaching the fluid management of a pediatric patient in the operating room, it is important to include all three sources of fluid loss in the fluid replacement calculation.

Fasting

The entire issue of preoperative fasting has undergone significant change that has markedly improved the fluid balance status of children before anesthetic induction.[17] A number of studies have examined the gastric residual volume in children who have fasted for 2 to 8 hours. Clear fluids (apple juice, water), administered in varying quantities from 3 mL/kg to ad lib up to 2 hours before scheduled surgical procedure, result in a gastric residual volume that is no different in volume or pH compared with that in children who have had standard fasting.[53, 73, 76, 84–87] These findings have resulted in a significant alteration in fluid management as can be seen in Table 1. The net effect of this altered fasting regimen is that children are arriving in the operating room less dehydrated and perhaps less irritable because they are not hungry. This is advantageous to the parents and the child. Although no studies have confirmed this, our clinical experience suggests that the incidence of hypotension during the gaseous induction of anesthesia is less in those children who have received this type of fluid management rather than the standard and now old-fashioned fasting regime. Another advantage of this new

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Table 1. *Fasting Guidelines (Hours)*

	MILK/SOLIDS		CLEAR LIQUIDS	
	Old	*New*	*Old*	*New*
Newborn to 6 months	4	4	2	2
6–36 months	6	6	6	3
>36 months	8	8	8	3

fasting guideline is that there is less chance of clinically significant hypoglycemia because the patient who has fasted excessively is now rarely presenting to the operating room.[1, 38, 93, 96, 97] This completely negates the need for any glucose-containing solutions for the majority of pediatric operative procedures.

Maintenance Fluid

The classic work of Holliday and Segar[36] demonstrated that most children require 100 mL/kg for the first 10 kg/24 hours, 50 mL/kg for weight between 11 and 20 kg/24 hours and 20 mL/kg/24 hour period for each kilogram above 20 kg in body weight. This generally is converted to a simple maintenance rate formula of 4 mL/kg/h for each kilogram less than or equal to 10, 2 mL/kg/h for each kilogram above 10 kg, and 1 mL/kg/h for each kilogram above 20 kg. For example, if a child weighed 15 kg, that child would receive 4 mL × 10 kg = 40 mL + 2 mL × 5 kg = 10 mL for a total maintenance rate of 50 mL/h (Table 2). Although this is a rather simplified approach to maintenance fluid therapy, it is nearly identical to that calculated through the standard Holliday and Segar formula.

Third Space Losses

Whenever a child is undergoing an operative procedure, edema formation as well as evaporative losses will take place. The larger the operative field, the greater the evaporative losses. For example, the evaporative losses from an inguinal herniorrhaphy would be almost negligible, whereas those associated with a major laparotomy and bowel resection would be very significant.[59, 79, 80] In addition to evaporative losses, whenever there is manipulation of tissue, edema results; this necessitates additional intravenous fluid in order to maintain intravascular volume equilibrium. Therefore, an intravenous fluid therapy management plan must also consider the type of operative procedure. In general, for a simple operative procedure involving minimal tissue manipulation, one would not administer additional fluid. For a procedure with moderate manipulation of tissues such as a laparotomy for simple bowel resection one would add 2 to 5 mL/kg/h. For a major operative procedure or large exposure of visceral surfaces, one would add 5 to 10 mL/kg/h. Where there is extensive manipulation of bowel such as multiple bowel resections or major reconstructive surgery, one would add 10 to 15 mL/kg/h for third space losses.[30] Thus, the calculated hourly operating room maintenance fluid could be formulated according to the following guidelines: For the first hour, one

Table 2. *Hourly Maintenance Fluid Requirements*

WEIGHT (KG)	ML/KG
Newborns to 10 kg	4 mL
10–20 kg	40 mL + 2 mL for each kg above 10 kg
>20 kg	60 mL + 1 mL for each kg above 20 kg

Table 3. *Fluid Replacement Prescription*

	DEFICIT	MAINTENANCE	THIRD SPACE (ML/KG/H)	BLOOD LOSS (ML/ML BLOOD)
First hour	½	See Table 2	2–15	2–3
Second hour	¼	See Table 2	2–15	2–3
Third hour	¼	See Table 2	2–15	2–3
Fourth hour	—	See Table 2	2–15	2–3

*In select cases, 5% albumen can be substituted for lactated Ringer's solution to replace blood loss (milliliter for milliliter) and to reduce the clear fluid administered to make up for third space losses in order to decrease edema formation; see text for details.

would make up half of the fluid deficit plus the maintenance rate plus the estimated third space losses. For the second hour, one would administer one quarter of the deficit fluid plus the maintenance plus the third space losses, and for the third hour, one would administer the remaining quarter of the fluid deficit plus maintenance and third space losses (Table 3).

Choice of Intravenous Fluid Therapy

Previous anesthetic practice generally recommended the administration of glucose-containing solutions to all pediatric patients coming to the operating room.[30, 36, 38, 96] This often resulted in a high glucose load at the beginning of the anesthetic procedure and occasionally a high osmotic load that was potentially dangerous for the pediatric patient. However, careful studies examining the actual incidence of hypoglycemia have found that the average healthy pediatric patient coming to the operating room, even with extended fasting, does not develop hypoglycemia.[1, 93, 97] Infants less than 10 kg in weight and those with debilitating diseases are the most likely candidates to develop hypoglycemia from excessive fasting.[96] Additionally, the serum glucose levels rise rather than fall during most operative procedures, probably due to the endocrinologic responses to the stress of surgery and anesthesia. It is for this reason that some pediatric anesthesiologists have advocated using glucose-free solutions such as lactated Ringer's for all maintenance, third space, and deficit fluid therapy, while advocating infusion of D_5 half-normal or $D_{2.5}$ half-normal saline to make up for maintenance fluid losses.[97] The glucose-containing fluid is administered as a constant infusion, "piggy backed" into the IV, so that glucose is administered slowly, therefore avoiding an excessive rapid glucose load. With the new fasting guidelines, however, the potential for clinically important hypoglycemia has been further reduced, and therefore, many pediatric anesthesiologists have changed their intravenous fluid therapy to lactated Ringer's solution without any exogenous glucose for the vast majority of operative procedures. For longer operative procedures, it is generally recommended to measure blood glucose values and determine the need for exogenous glucose therapy according to the measured glucose values. Neonates, especially those in the first 7 days of life, almost universally require a constant glucose infusion.

Another reason for the change to nonglucose-containing solutions, is that there are animal and human data suggesting a greater area of cerebral damage in patients (animals) who have a high blood glucose level at the time of a hypoxemic insult.[28, 43, 69, 81] Although intraoperative cardiac arrest and prolonged hypoxemic insult are rare in the pediatric patient, it appears that there may be an advantage in avoiding hyperglycemia. The change in fasting guidelines, combined with the change in recommended intravenous fluid therapy, minimizes the chances of excessive glucose administration even during long operative procedures.

ASSOCIATED CONCERNS DURING INTRAVENOUS FLUID THERAPY

Volume-Limiting Techniques

Another area of concern to the pediatric anesthesiologist is methods for limiting the amount of fluid administered, particularly to the neonate or infant. Therefore, the use of rate-limiting devices, e.g., pumps or volume-limiting devices (no more than 1 hour of fluid contained in the burette) will decrease the possibility of accidental and massive bolus fluid administration. Such devices are recommended for fluid administration to all children under 10 years of age. The use of intravenous fluid containers that are limited in volume to 250 mL may minimize accidental bolus administration; even if the IV were to be accidentally left open, the total volume administered could not exceed 250 mL.

Air Emboli

A further concern of intravenous fluid therapy is the possibility of accidental air embolization. This is particularly important when caring for neonates or children with structural intracardiac defects. It is extremely important to purge all air from intravenous lines before attachment to an intravenous catheter and to aspirate each injection port carefully, in order to clear all air from the system. In addition, whenever injecting intravenous medications, one should point the syringe upward and eject any air that might be contained within the hub of the needle or the injection site of the IV tubing prior to intravenous drug injection. For newborns who will be undergoing procedures with minimal chance for the need of a blood transfusion, the use of air traps may be of value in preventing air embolization. Another concern for the anesthesiologist, however, is that fact that the majority of accidental needle punctures is directly related to the use of needles and the recapping of needles following administration of medications.[47] For adults, it is generally recommended to avoid the use of needles by inserting a three-way stopcock into the intravenous system.[33] For pediatric patients, however, this is less acceptable because it increases the chance of fluid overload because of the necessity to "flush" such medications through the system to the patient; it is more likely that air might be introduced into the system. For the very young pediatric patient, it is generally recommended to have an injection port immediately over the end of the intravenous catheter so that there is minimum dead space in the system. However, this necessitates the use of a needle to administer the medication. Caution is advised whenever using needles to administer medications especially if recapping of the needles is required.

Intravenous Access

Whenever caring for the pediatric patient, one of the more difficult aspects of this care may be the insertion of an adequate intravenous catheter for the proposed operative procedure. The use of a needle for the induction of anesthesia is perfectly adequate; however, a plastic catheter inserted within the vein is a much more stable and desirable route of fluid administration. Fortunately, intravenous catheters are now available down to 26 gauge, which may be readily inserted even in the smallest of infants. The small 24- and 26-gauge catheters, however, may seriously impede the ability to administer blood rapidly but are perfectly adequate for the rapid administration of crystalloid, 5% albumin, and fresh frozen plasma (FFP).[11, 66] If one needs to establish a larger size intravenous access, one may make use of large veins such as the external jugular, the internal jugular, or the femoral vein. These veins may be accessed by use of the wire through a needle technique (Seldinger).[22]

BLOOD PRODUCT MANAGEMENT

Management of blood products in pediatric patients has undergone extensive changes in the last 15 years primarily due to advances in blood banking, blood salvage techniques, the almost exclusive use of component therapy, and preoperative autodonation and directed donor blood.[26, 44, 52, 64, 88, 92] Perhaps nothing has changed the approach to blood transfusions to a greater extent than the acquired immunodeficiency syndrome epidemic and the fear of transmitting the human immunodeficiency virus (HIV).[3, 65] Despite very sophisticated screening tests as well as cautious blood banking techniques, it is still possible to transmit HIV through the transfusion of blood that has tested negative.[24, 95] The incidence of such false-negative tests is estimated to be 20 U/1 million U transfused; this incidence may also have geographic variation.[77] Therefore, it is in the patient's best interest to minimize exposure to blood products and in the physicians best interest to document the need for the transfusion of each blood product.

Blood Volume Estimation

Whenever a child presents for a surgical procedure, it is important to estimate the child's blood volume and the maximal allowable blood loss, to determine the minimal acceptable hematocrit for that particular patient, and to have an appropriate volume of blood products available for the scheduled surgical procedure.

The circulating blood volume of a pediatric patient is age dependent. The premature infant will have a blood volume of approximately 90 to 100 mL/kg, the term infant 80 to 90 mL/kg, children 3 months to 1 year of age 70 to 80 mL/kg, and children greater than 1 year of age approximately 70 mL/kg. Obviously, the extremely obese child would have a smaller circulating blood volume by weight. The minimal acceptable hematocrit will depend on a number of factors such as metabolic demand, the ability to deliver oxygen to tissues (cardiac output), the presence or absence of a cardiac or pulmonary shunt, and the distribution of that cardiac output to normal or compromised vascular beds.[32, 34, 41, 51, 55, 60, 62] Specific populations of patients might require a higher hematocrit, e.g., those with severe pulmonary disease, cyanotic congenital general heart disease, or the premature infant.[39] Conversely, the perfectly healthy child will tolerate hematocrits well below the previously sacrosanct 30%; providing the circulating blood volume is maintained, most pediatric patients will tolerate a hematocrit of 20% to 25%. Although there are several methods for estimating a patient's blood volume, the easiest method is to use a simple proportion.[4, 30, 40]

Maximum allowable blood loss (MABL) may be calculated as follows:

$$\text{MABL} = \frac{\text{estimated blood volume} \times (\text{starting patient hematocrit} - 25)}{\text{starting patient hematocrit}}$$

An example would be the 15-kg child who would have an estimated blood volume of 15 × 70 mL/kg = 1050 mL. If the patient's starting hematocrit were 45, the MABL would be

$$\frac{1050 \times (45 - 25)}{45} \div \frac{1050 \times 20}{45} = \text{approximately } 465 \text{ mL.}$$

Once one has calculated the MABL, one can then initiate volume replacement that is directed at replacing deficit and maintenance fluids, third space losses, as well as blood loss. Shed blood may be replaced in two ways: either milliliter per milliliter with 5% albumin or 2 to 3 mL of balanced salt solution (lactated Ringer's) per milliliter of shed blood. In general, shed blood can be most economically replaced with balanced salt solution without significant morbidity to the pediatric patient. For certain types of procedures such as neurosurgical procedures in which one wishes to minimize the amount of free water that might result in cerebral edema, one may choose to replace shed blood milliliter for milliliter with 5% albumin. Perhaps in the neonate, who may have difficulty in handling a large fluid load or perhaps in the child who will undergo several blood volume changes, one may consider using 5% albumin once the patient has shed one-quarter to one-half blood volume. Large volumes of crystalloid may also be problematic during extensive procedures involving bowel manipulation; excessive fluid therapy in this circumstance may make bowel anastomosis or abdominal closure more difficult due to bowel edema.[68]

In the previous example, in the child with a blood volume of 1050 mL and an estimated MABL of 465 mL, replacement of blood lost up to that point could be made with either 900 to 1400 mL of lactated Ringer's or 465 mL of 5% albumin. If blood loss continues well beyond the MABL then replacement of red blood cells (RBCs) must be considered so as to maintain the hematocrit within an acceptable range. Once a patient has been exposed to a unit of packed RBCs (PRBCs), there is probably little additional danger of disease transmission whether a small or large portion of that unit has been transfused. Therefore, it is our practice to administer as much of that unit of PRBCs as will be safely tolerated rather than expose the patient to an additional unit of blood product postoperatively. For the majority of pediatric patients, we replace the entire MABL with balanced salt solutions. When blood loss exceeds the MABL, replacement may be made with PRBCs and balanced salt solution. The hematocrit of PRBCs is approximately 70%; therefore, for each 100 mL infused, 70 mL will be RBCs. If the estimated blood loss exceeded the MABL by 200 mL, then replacement of that 200 mL of blood would be made according to the following formula:

1. Volume of blood to replace (200 mL) × desired hematocrit (Hct) (30) = 60 mL of 100% RBCs.
2. The hematocrit in PRBCs = 70%.
3. Therefore, 60 mL ÷ 0.70 = 85 mL. Eighty-five milliliters of PRBCs (Hct 70) is equivalent to 200 mL whole blood (Hct 30).

This can be simplified by transfusing approximately 0.5 mL PRBCs for each milliliter beyond the MABL.

Component Therapy

The anesthesiologist must consider percentages of blood volume rather than units of blood transfused. The reason it is important to use this concept is that one adult unit of blood (500 mL) represents 10% of the blood volume of the average 70-kg adult (70 mL × 70 kg = 4900 mL), but it will represent nearly 100% of the blood volume of a 7-kg child (70 mL × 7 kg = 490 mL). The metabolic effects of that unit of transfused blood product will be proportionally greater in the young pediatric patient compared with the adult. Therefore, for the pediatric patient one must think in terms of blood volumes and portions of blood volumes transfused rather than units of blood product transfused.

Red Blood Cells

RBCs are available in several forms, i.e., frozen PRBCs, citrated PRBCs, citrated whole blood, or fresh whole blood. Frozen PRBCs are the most expensive blood product but have the theoretical advantages of less blood group sensitization, better preservation of 2,3 diphosphoglycerate (2,3 DPG), less potential for transmission of viral diseases, a smaller citrate load, and perhaps a smaller exposure to potassium that has leaked from the RBCs.

Fresh Frozen Plasma

Fresh frozen plasma (FFP) contains all clotting factors except platelets. FFP is generally administered intraoperatively to replace coagulation factors lost during massive blood transfusion. FFP contains the highest proportion per unit volume of citrate of any blood product available for transfusion and may therefore present the problem of citrate toxicity (acute ionized hypocalcemia) when rapidly administered to small pediatric patients. The indications for FFP during massive transfusion will be considered later. FFP is occasionally recommended for the treatment of von Willebrand's disease or hemophilia B. However, most patients with von Willebrand's disease will respond to desmopressin (DDAVP).[72] We generally withhold FFP transfusion until the surgical procedure has begun, while observing the surgical field for adequacy of hemostasis and communicating with the surgeon to determine the true need for FFP transfusion.

Platelets

Platelet therapy generally is required in patients with drug-induced thrombocytopenia and during massive surgical blood loss.[31] In general, a patient whose platelet count has fallen gradually over time will have a lower platelet requirement than the patient who has sustained a rapid blood loss and dilution of platelets (dilutional thrombocytopenia). For example, patients whose platelet counts have gradually fallen to the 10,000 to 20,000/mm^3 range do not generally require additional platelets unless there are signs of clinical bleeding or a surgical procedure is needed.[31] Conversely, those patients whose platelet count has fallen to the 50,000 to 75,000/mm^3 range during rapid blood loss and subsequent replacement, will generally demonstrate pathologic bleeding with a platelet count in the range of 50,000 to 75,000/mm^3.[13, 23, 45, 56, 57, 63] There are no clear-cut guidelines that relate platelet count and clinical bleeding. The anesthesiologist must assess each patient individually, while observing the surgical field for evidence of pathologic (nonsurgical) bleeding.

Occasionally, a patient will present for an urgent or semiurgent surgical procedure with a prolonged bleeding time and a recommendation is made to transfuse platelets before surgery. It is our practice to have the platelets available in the operating room but avoid transfusion unless the patient demonstrates the need for platelets with abnormal bleeding in the surgical field. An exception to this recommendation is the patient having a surgical procedure in which the successful outcome is dependent on complete hemostasis, e.g., neurosurgical procedures. Generally, a transfusion of 0.1 to 0.3 U of platelets per kilogram will result in an increment in platelet count of 20,000 to 70,000/mm^3. It has been our experience in patients with massive ongoing blood loss that the higher dose (0.3 U/kg) is more efficacious than a lower dose (0.1 U/kg) of platelets.[23]

If platelets must be administered, e.g., if the patient is beginning with a low platelet count, it is important to administer them just before the surgical procedure to ensure the highest possible levels at the time of peak demand. A special large-pore filter should be used since micropore filters will absorb the majority of platelets.[50] One must also recall that a considerable amount of FFP is contained in platelet concentrates that may partially replenish shed coagulation factors and therefore diminish the need for FFP.

MASSIVE BLOOD TRANSFUSION

Massive blood transfusion is defined as replacing the patient's entire blood volume one or more times. This concept (blood volumes rather than units of blood lost) is particularly important for the pediatric patient. If one understands the composition of each blood component, one may anticipate associated problems when large quantities of these blood products are transfused. The major problems associated with massive blood transfusion are related to coagulopathy and metabolic abnormalities from storage: derangements of potassium and calcium homeostasis, hypothermia, abnormalities of acid–base balance, and shifts of the oxygen/hemoglobin dissociation curve.

Coagulopathy

The coagulopathy of massive blood transfusion may be divided into two categories: (1) dilutional thrombocytopenia and (2) dilution of clotting factors. Dilutional thrombocytopenia depends on the starting platelet count, the volume of shed blood, and the presence or absence of a disseminated intravascular coagulopathy. Dilution of coagulation factors depends on the volume of shed blood, the type of blood transfused (whole blood, citrated PRBCs, frozen PRBCs) and the presence of a disseminated intravascular coagulopathy.

Clotting Factor Deficiency

Studies of adult trauma patients have found that clinical bleeding occurred in a small proportion of patients after 15 U of whole blood had been transfused in a small proportion of patients, but that by 30 U of whole blood transfused, all patients developed signs of clinical coagulopathy.[13, 56] When examined more carefully, this coagulopathy was unrelated to abnormalities of the prothrombin time (PT) or partial thromboplastin time (PTT), but did correlate with platelet counts of less than 65,000/mm^3.[45, 56, 57] The average male patient will have approximately a 5000 mL blood volume (70 mL/kg × 70 kg), which is roughly equivalent to 10 U of whole blood. Relating this to the pediatric patient, one would estimate that a small proportion of pediatric patients would develop coagulopathy after one blood volume, but that many pediatric patients would develop a coagulopathy after three blood volumes had been transfused (Fig. 1). However, *this only applies if the transfusions were made exclusively with whole blood,* and in this circumstance, the coagulopathy would have been primarily due to dilutional thrombocytopenia and not clotting factor deficiency. Citrated whole blood contains all blood components in normal concentrations except platelets and has a reduced concentration of labile factors V and VIII (approximately 20% to 50% of normal). In order for a coagulopathy secondary to dilution of clotting factors to develop, factors V and VIII must be severely reduced to between 20% and 30% of baseline.[56] Since whole blood has all clotting factors including the labile factors V and VIII in concentrations equal to or higher than this, it is unlikely that clotting factor deficiency will result despite extensive blood transfusions of three blood volumes or more, (if that blood replacement was made entirely with whole blood). However, modern blood banking rarely provides whole blood so that most shed blood is replaced with either citrated PRBCs or frozen PRBCs and crystalloid or 5% albumin. Since neither of these blood products contain significant volumes of clotting factors, *coagulopathy due to dilution of coagulation factors may result much sooner than if shed blood was replaced exclusively with whole blood.*[12, 14, 19, 35, 61] Therefore, dilutional clotting factor coagulopathy is highly likely to occur when blood loss exceeds 1.5 blood volumes (Fig. 1). There is some evidence to suggest that prolongations of the PT and PTT will occur at higher clotting factor values when multiple clotting factor deficiencies develop compared with isolated single clotting factor deficiencies.[14, 19, 61] Studies of adult patients have found a clear relation between dilution of clotting factors and volume of blood transfused. Moderate prolongations of the PT and PTT were found after one blood volume loss without significant clinical bleeding.[61]

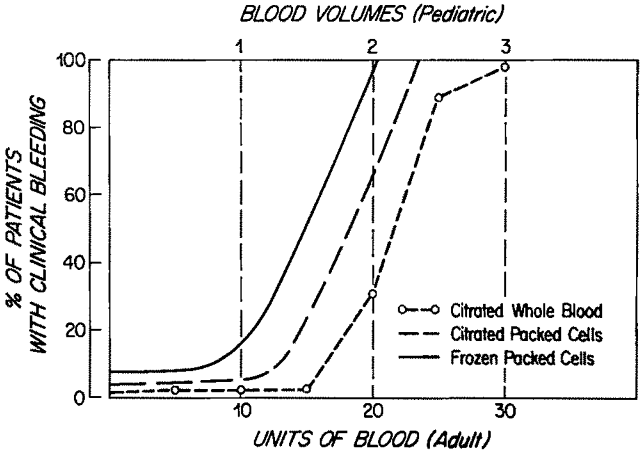

Figure 1. The broken line with open circles represents an adult study of citrated whole blood; bleeding in most cases was secondary to dilutional thrombocytopenia. Other lines represent postulated points of *clotting factor deficiency* if solely citrated packed red blood cells or frozen packed red blood cells are transfused. *Adapted from* Miller RD: Transfusion therapy and associated problems. ASA Refresher Courses in Anesthesiology 1:107, 1973; and Coté CJ, Blood replacement and blood product management. In: A Practice of Anesthesia for Infants and Children. Ryan JF, Coté CJ, Todres ID, Goudsouzian N, eds. Grune & Stratton, Inc., Orlando, FL, 1986.)

There are no published studies examining the issue of massive blood replacement in pediatric patients using component therapy exclusively. We have examined our experience in a number of patients who lost 0.5 blood volumes or greater and found none of the children developed signs of coagulopathy when blood loss was one blood volume or less and replacement made exclusively with citrated PRBCs or frozen PRBCs.[19] We did, however, observe signs of clinical coagulopathy in children whose blood loss was equal to or exceeded 1.5 blood volumes and, at that point, the PT and PTT were prolonged to greater than 1.5 times control. Our experience has been that children whose blood loss is equal to or less than one blood volume will have slight prolongations of the PT and PTT but that these abnormalities self-correct within 24 to 36 hours of the surgical procedure, provided significant blood loss does not continue into the postoperative period. Unfortunately, there are few data that clearly relate the change in PT and PTT with clinical coagulopathy. The consensus panel of the National Institutes of Health and others suggest that 1.5 times control should be considered pathologic and therefore may warrant correction with FFP transfusion.[6, 16]

Dilutional Thrombocytopenia

Studies of adult and pediatric patients have found that clinical bleeding correlates with a platelet count ≤ 65,000/mm^3.[13, 23, 45, 56, 57, 63] The decrease in platelet count, however, is less than one would predict with pure dilution; this may reflect increased platelet release from bone marrow, lungs, and lymphatic tissue (Fig. 2).[23, 45] In both adult and pediatric studies, it would seem that the platelet count will not decrease to this range until two or more blood volumes have been lost. Our studies in pediatric patients who lost one to five blood volumes found that clinical bleeding did not occur until platelet counts fell below 50,000/mm^3 despite blood losses as great as five blood volumes.[23] Furthermore, the starting platelet count was very

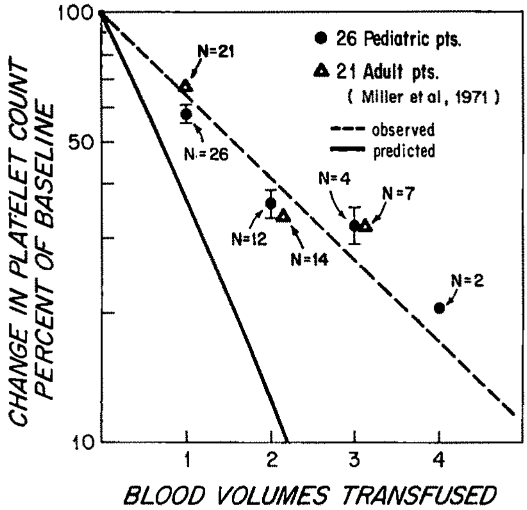

Figure 2. Percentage of change in platelet count versus blood volumes transfused in adults and children. (- - -), Observed values; (—), calculated values. This difference suggests mobilization of platelets during massive transfusion. *From* Coté CJ, Liu LMP, Szyfelbein SK, et al: Changes in serial platelet counts following massive blood transfusions in pediatric patients. Anesthesiology 62:197–201, 1985; with permission.)

important. If a patient started with a very high platelet count (600,000/mm^3 or greater), there was no need for platelet transfusion despite a five blood volume loss. Conversely, in patients who started with a low platelet count (100,000–150,000/mm^3) dilutional thrombocytopenia occurred after one blood volume was lost (Fig. 3*A* and *B*). Therefore, if a surgical procedure is scheduled in which extensive blood loss can be anticipated, it is important to obtain a baseline platelet count, so as to anticipate at what point during the surgical procedure one might require platelets. On average, a patient will have a platelet count 70% of baseline at one blood volume loss, 40% of baseline after two blood volumes lost, and 20% of baseline after three blood volumes lost. Prophylactic transfusions are not indicated without clinical evidence of microvascular bleeding and ongoing blood loss.[23, 70]

In summary, if massive transfusions are made exclusively with whole blood, there is little likelihood that FFP will be required, but there may be a need for platelet transfusion and this depends on the starting platelet count. Conversely, if extensive blood loss is replaced with PRBCs exclusively, then FFP may be required at approximately 1.5 blood volume loss. Platelet needs are unrelated to the chosen type of blood product replacement.

Hyperkalemia

Hyperkalemia appears to be primarily a problem of transfusions with whole blood.[49] Cardiac arrest has been reported in neonates undergoing exchange transfusion with 2-day-old whole blood having high potassium values.[74] Even relatively fresh whole blood may have a high potassium value. If whole blood is to be transfused into neonates or infants, even if fresh, the potassium value should be quantitated before transfusion, particularly if the volume of blood transfused will represent a large fraction of the infant's circulating blood volume.

Citrated or frozen PRBCs may have supernatant potassium concentrations in excess of 60 mEq/L.[25, 98] However, clinically important hyperkalemia has not been observed following routine transfusion. Although one of the reported advantages of frozen PRBCs is a low potassium value, the greater the time between thawing and administration, the higher the supernatant potassium value. Our experience with children suffering from extensive thermal injuries requiring two to three blood volume transfusions with exclusively frozen PRBCs and FFP, have not revealed any cases of clinically important hyperkalemia.

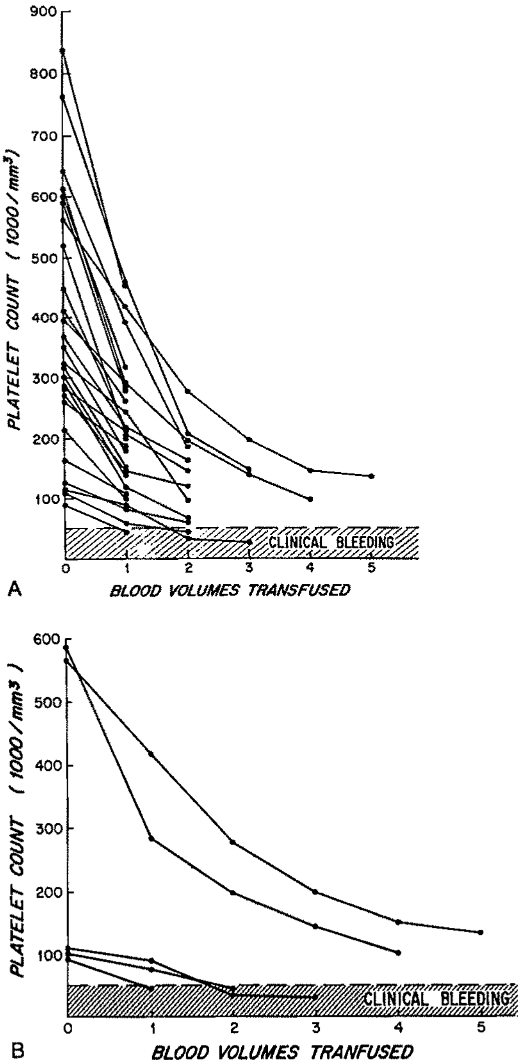

Figure 3. *A*, Data from 26 pediatric patients who lost 1 to 5 blood volumes. The baseline platelet count is invaluable in estimating potential platelet needs in relation to blood volumes transfused. A low initial count suggests the need for early exogenous platelet transfusion, whereas a high initial platelet count indicates that exogenous platelets may not be required until several blood volumes have been lost. *B*, The platelet counts from five patients were separated from A. The three patients who developed a coagulopathy began surgery with a relatively low platelet count, whereas the two patients with a very high platelet count did not require platelet transfusion despite the loss of 4 and 5 blood volumes. (*Adapted from* Coté CJ, Liu LMP, Szyfelbein SK, et al: Changes in serial platelet counts following massive blood transfusions in pediatric patients. Anesthesiology 62:197–201, 1985; with permission.)

With the increasing use of directed donor blood and self-donation, there is an increased use of whole blood products. We recently observed a teenaged patient who had donated several units of his own blood before Harrington rod instrumentation, who received 2 U of whole blood over 30 minutes; his serum potassium rose from 3.5 to 6.3 mEq/L. This was diagnosed incidentally when the serum potassium was measured in conjunction with arterial blood gases; the child did not require any treatment. However, it emphasizes that hyperkalemia of clinical importance may occur with the rapid transfusion of whole blood, particularly old whole blood, i.e., greater than 14 days old.

A recent case report of an adult patient suffering a hyperkalemic cardiac arrest during rapid transfusion with a special rapid transfusion device (Level 1, Marshfield, MA) suggests that hyperkalemia may occur even with component therapy if the transfusion is sufficiently rapid.[37] Further studies are needed in order to more carefully delineate the severity of this problem. It would seem that the pediatric patient at greatest risk for this problem would be a small patient who is receiving a very rapid transfusion.[2, 7]

Hypocalcemia

Ionized hypocalcemia (citrate toxicity) is a problem associated with the binding of ionized calcium (Ca^{++}) by the sodium citrate preservative.[9] The two blood products with sufficient concentrations of citrate present to cause this problem are whole blood and FFP. Ionized hypocalcemia has been associated with depressed cardiac function and therefore should be avoided if possible.[89] FFP contains more citrate per unit volume than whole blood (80% of the citrate in whole blood is left in the FFP fraction following separation). Therefore, FFP is the most likely blood product to cause clinically important hypocalcemia in infants and children where a unit of FFP constitutes a significant proportion of the circulating blood volume. This is particularly important in patients undergoing surgical procedures who already have a low Ca^{++}.

We have examined the alterations in Ca^{++} that followed rapid transfusions of FFP equivalent to 1 to 2.5 mL/kg/min for 5 minutes in children with extensive thermal injury. The maximal change in Ca^{++} occurred at 5 minutes.[21] Despite the fact that there were highly significant reductions in Ca^{++} there were no consistent adverse cardiovascular events (Fig. 4). A laboratory study examining the interaction between halothane anesthesia and ionized hypocalcemia found greater cardiovascular depression when citrate was administered during deeper compared with lighter levels of halothane anesthesia.[18] Further laboratory studies using an isolated heart model suggest that ionized hypocalcemia and halothane anesthesia, by themselves, will have significant myocardial depressant effects but when added together, the myocardial depression is potentiated, i.e., the depression observed was greater than with either factor by itself.[8, 71] It appears that the calcium-channel blocking

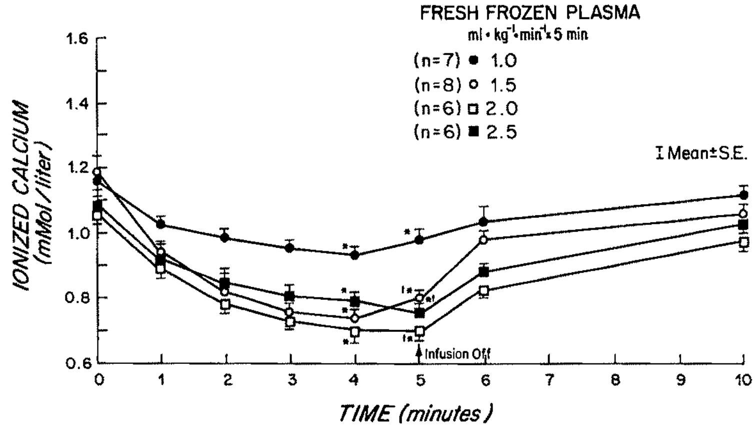

Figure 4. Changes in arterial ionized calcium in children with severe thermal injuries during fresh frozen plasma infusions of 1.0 to 2.5 mL/kg/min for 5 minutes through an infusion pump. Note the dangerous though transient fall in ionized calcium with the nadir occurring between the fourth and fifth minutes. Ionized hypocalcemia will occur whenever the infusion rate equals or exceeds 1.0 mL/kg/min. (From Coté CJ, Drop LJ, Hoaglin DC, et al: Ionized hypocalcemia after fresh frozen plasma administration to thermally injured children: Effect of infusion rate, duration, and treatment with calcium chloride. Anesth Analg 67:152–160, 1988; with permission.)

properties of inhalation agents are potentiated during periods of ionized hypocalcemia.

It has been stated that calcium chloride is preferable to calcium gluconate because calcium chloride does not require hepatic metabolism to free the gluconate moiety. We have examined the changes in Ca^{++} as well as hemodynamic responses to bolus administration of equimolar concentrations of calcium gluconate and calcium chloride in both children and animals (Figs. 5 and 6).[20] We found the rate of ionization of calcium gluconate was equivalent to the rate of ionization of calcium chloride and the cardiovascular responses were similar. More importantly, the animal studies found no significant advantage after 2 minutes between large boluses of calcium chloride or calcium gluconate (Fig. 5*A*) compared with smaller doses of calcium chloride or gluconate (Fig. 5*B*). This suggests that the treatment of ionized hypocalcemia would be safer and more efficacious with frequent small boluses rather than intermittent large boluses of calcium.

It is our clinical impression that rapidly administered FFP is more likely to have adverse cardiovascular effects when administered directly into a central venous catheter due to high citrate concentrations (blood with low Ca^{++}) being delivered to the coronary circulation. We prefer to administer FFP through a peripheral intravenous site, if possible. Whenever the rate of infusion exceeds or equals 1.0 mL/kg/min, exogenous administration of calcium should be considered *during the transfusion* so as to avoid dangerous hypocalcemia. This is particularly important in caring for neonates and small infants in whom it is relatively easier to administer a large bolus of FFP over a brief period of time; it is also an important concern in patients with impaired hepatic blood flow (impaired citrate metabolism), such as liver transplant patients, cardiac surgical patients, and neonates (Fig. 7).[48]

Acid–Base Balance

Most blood products have a pH of 6.6 to 6.9. The majority of this pH change is due to a rise in carbon dioxide concentration secondary to the continued metabolism of the red cells after donation. Once available oxygen stores have been used, anaerobic metabolism continues, resulting in lactate production. However, hemoglobin and bicarbonate rapidly counteract the majority of the lactic acid; if a patient has a normal blood volume, it is unlikely that the patient will require exogenous bicarbonate therapy.[15, 58] If, however, the patient arrives in the operating room in shock, the patient will already have a metabolic acidosis and in this circumstance, exogenous sodium bicarbonate may be indicated. One must recall that the sodium citrate will be metabolized to form bicarbonate, resulting in a metabolic alkalosis 1 to 4 hours after extensive transfusion of citrated blood products.[27] Therefore, one must avoid adding to this metabolic load and only administer sodium bicarbonate if there is a measured and severe metabolic acidosis.

Hypothermia

Hypothermia is frequently associated with procedures involving massive blood loss due both to the size of the surgical field exposed to the atmosphere as well as the need for rapidly transfusing cold blood products that have not had sufficient time to be warmed. Hypothermia will have significant effects on the oxygen/hemoglobin dissociation curve, causing a leftward shift that will result in oxygen being bound more tightly to hemoglobin and therefore less available for delivery to tissues.[5, 94] It is important to use blood warmers as well as any other modality to maintain patient temperature so as to avoid hypothermia, i.e., warming blankets, radiant warmers, plastic wrap around extremities, a heated humidifier in the anesthesia circuit, and covering the patient's head. Covering the head is particularly helpful in pediatric patients. New rapid transfusion devices have markedly improved the thermodynamics of rapid transfusions with cold blood products; such devices

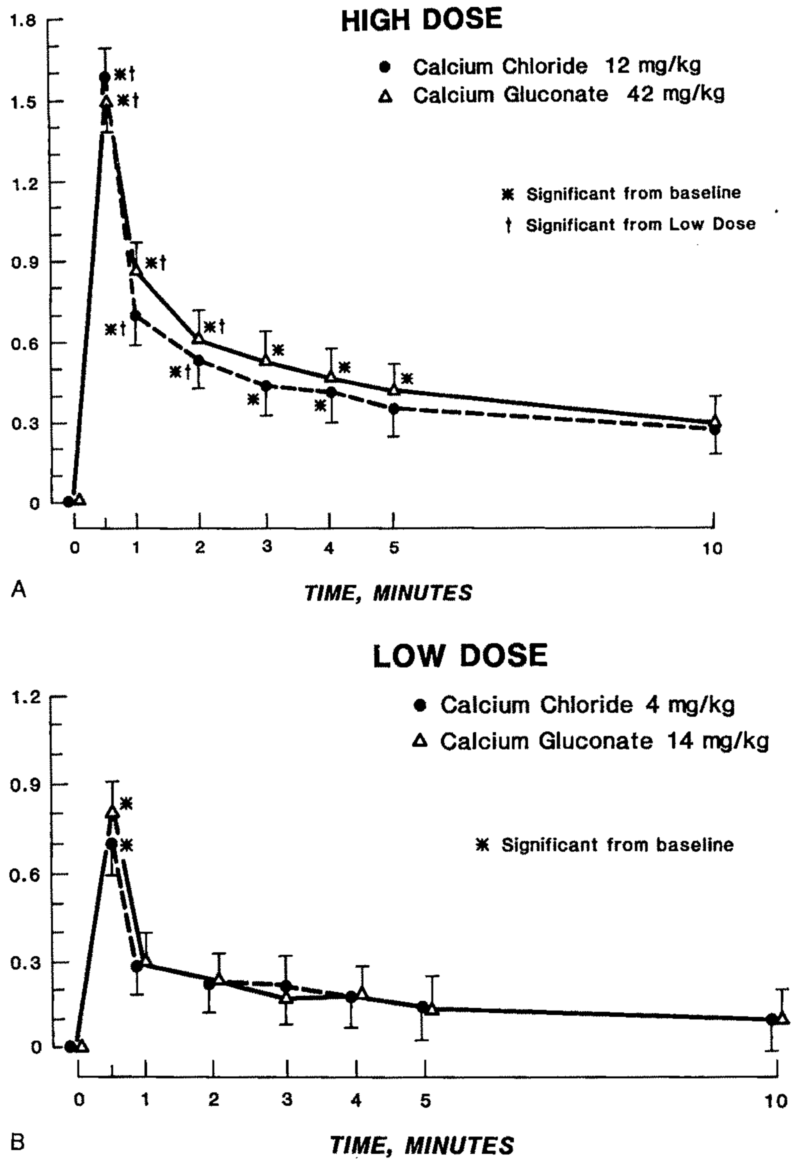

Figure 5. Changes in arterial ionized calcium in dogs who received equipotent doses of calcium chloride and calcium gluconate. At 30 seconds both forms of calcium have dissociated equally; these data indicate that hepatic metabolism of the gluconate moiety is not required to liberate ionized calcium from calcium gluconate. There was no significant difference in Ca^{++} between the high (*A*) and low (*B*) dose after 2 minutes. This suggests that frequent small boluses may be safer than single large boluses. (*From* Coté CJ, Drop LJ, Daniels AL, et al: Calcium chloride versus calcium gluconate: Comparison of ionization and cardiovascular effects in children and dogs. Anesthesiology 66:465–470, 1987; with permission.)

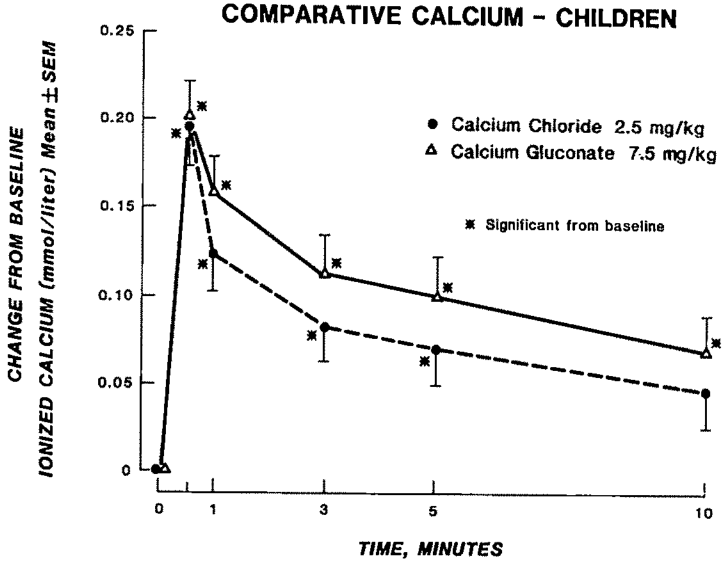

Figure 6. Changes in ionized calcium in 10 children with thermal injuries following equipotent doses of calcium chloride and calcium gluconate. At 30 seconds and throughout the study period there was no difference between the two forms of exogenous calcium therapy. (*From* Coté CJ, Drop LJ, Hoaglin DC, et al: Ionized hypocalcemia after fresh frozen plasma administration to thermally injured children: Effect of infusion rate, duration, and treatment with calcium chloride. Anesth Analg 67:152–160, 1988; with permission from the International Anesthesia Research Society.)

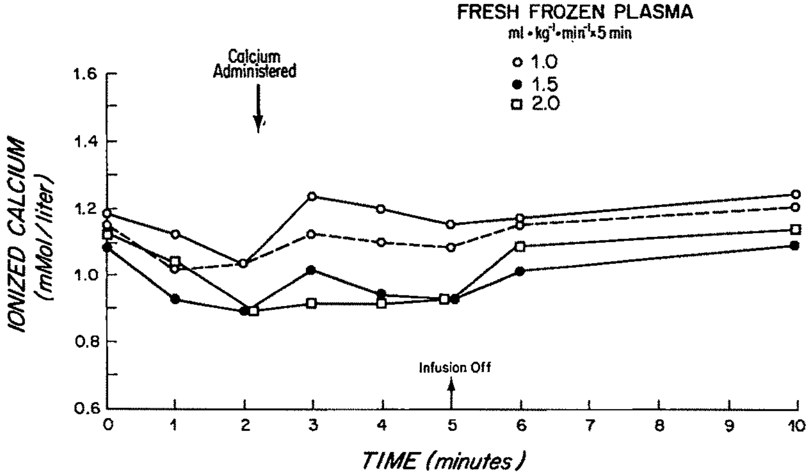

Figure 7. The change in ionized calcium in four thermally injured patients who received calcium chloride after 2 minutes of FFP infusion is shown *(arrow)*. Note that there were no sharp increases or decreases in Ca^{++}. (*From* Coté CJ, Drop LJ, Hoaglin DC, et al: Ionized hypocalcemia after fresh frozen plasma administration to thermally injured children: Effect of infusion rate, duration, and treatment with calcium chloride. Anesth Analg 67:152–160, 1988; with permission from the International Anesthesia Research Society.)

are extremely helpful in the management of trauma patients and during liver transplants and major reconstructive or oncologic surgical procedures.[67]

Oxygen/Hemoglobin Dissociation

Hypothermia will cause a left shift of the oxygen/hemoglobin dissociation curve. Metabolic alkalosis will cause a further leftward shift of the oxygen/hemoglobin dissociation curve.[10] It is emphasized that exogenous bicarbonate should not be administered unless there is a clearly measured lactic acidosis. In addition, a low 2,3 DPG will result in a left shift of the oxygen/hemoglobin dissociation curve.[78, 99] This certainly is associated with transfusion of large volumes of citrated whole blood and FFP; oxygen/hemoglobin dissociation is less affected by transfusion with citrated PRBCs or frozen PRBCs. Frozen PRBCs would appear to offer the greatest advantage in minimizing this leftward shift of the oxygen/hemoglobin dissociation curve since there is no citrate and 2,3 DPG is preserved. The clinical importance of this leftward shift is less clearly defined, particularly in the pediatric patient.[99]

SUMMARY

The management of fluid, electrolyte, and blood component therapy is dependent on a thorough understanding of the surgical procedure involved, estimates of the patient's blood volume, knowledge of the metabolic derangements associated with specific blood components, and an understanding of the differences between infants, children, and adults. With this knowledge, one can anticipate the types of problems that may develop and the volumes of blood loss at which they might appear during massive transfusions. This allows one to take appropriate precautions to avoid or effectively treat potentially serious complications. One must take whatever measures are necessary to minimize unnecessary blood transfusions and apply all modern anesthetic techniques such as predonation, blood scavenging, autotransfusion, controlled hypotensive anesthesia, and normovolemic hemodilution when appropriate.[29, 42, 46, 54, 82, 90, 91]

All of these techniques require significant experience as well as a clear understanding of the physiology and pharmacology involved. The physician must always be in a position to weigh benefits versus risks for the anesthetic technique chosen to reduce blood loss or the need to administer a blood product. However, one must be prepared to defend the administration of any blood product, and this is best accomplished by documenting the reason for that transfusion in the anesthetic record. With improved diagnostic capabilities, i.e., rapid in-operating-room estimations of the PT, PTT, and improved measurements of platelet counts, the anesthesiologist will be in a better position to determine on a more scientific basis the need for specific blood product administration.

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Perioperative Apnea in the Preterm Infant

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As the survival rate of preterm infants (defined as an infant 37 weeks or less gestational age at birth) increases, an ever increasing number of former preterm infants are presenting for anesthesia and surgery. While some are critically ill and require immediate and often multiple operations to survive, most of these infants are relatively healthy and require only minor elective surgery that can be scheduled at any time. However, when anesthesia and surgery are undertaken in the first year of life, preterm infants are at increased risk of developing respiratory and cardiovascular complications during the perioperative period, the most common and most serious of which are apnea, periodic breathing (PB), and bradycardia.[8, 12, 28, 37]

Inguinal hernias are particularly common in former preterm infants (defined as an infant <37 weeks gestational age at birth whose postconceptual age, defined as the sum of gestational and postnatal age, exceeds 37 weeks) with an incidence of 13% among those less than 32 weeks gestational age at birth.[30] Because of the high risk of incarceration, early surgical repair of the hernia is usually recommended. Former preterm infants with this condition are usually healthy otherwise and therefore provide an excellent opportunity for the study of the incidence of serious perioperative complications. In this article, we summarize the findings of several investigators who have performed retrospective and prospective studies of risks associated with herniorrhaphy and other surgical procedures in former preterm infants during the first year of life. We also present a summary of our own recent work in this area, which includes the perioperative use of caffeine for the prevention of postoperative apnea, the effects of spinal and general anesthesia on the incidence of postoperative apnea and bradycardia, and an examination of the possible contribution of anemia of prematurity to operative risk.

REVIEW OF THE LITERATURE

Because of their immature organ systems, preterm infants represent a significant operative risk.[12] Respiratory function in these infants is a major concern; the incidence of apneic episodes in the preterm infant is inversely related with postconceptual age. One of the explanations for this phenomenon was offered by

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Henderson-Smart et al,[19] who demonstrated that the auditory brainstem conduction time increased as gestational age decreased and that the increase in conduction time correlated with the frequency of apneic episodes. These authors concluded that apnea is probably related to immature brainstem function. Several other plausible explanations may account for the high incidence of postoperative apneas in former preterm infants including reduced fraction of type I fibers in the diaphragm.

While prolonged apnea is always pathologic, PB has been observed to occur in 30% to 95% of otherwise healthy preterm infants during sleep. PB reflects inadequate development of ventilatory control.[24] Some preterm infants with PB demonstrate hypoventilation, a shift to the right of the CO_2 response curve, and a paradoxical response to hypoxia. During PB, there is a gradual reduction in ventilation and oxygenation that may lead to prolonged apnea.[31] Kelly and Shannon[24] reported a marked increase in PB in infants with near-miss sudden infant death syndrome.

Preterm infants who have undergone general anesthesia are prone to develop apnea, PB, and bradycardia.[26, 28, 37, 43] Following a retrospective chart review of healthy infants undergoing herniorrhaphy, Steward[37] concluded that preterm infants undergoing surgery in the first months of life are more likely to develop respiratory complications during and following anesthesia than are full-term infants. Twelve per cent of the preterm infants in this study had apnea during anesthesia and in the first 12 postoperative hours. None required postoperative mechanical ventilation.

Liu et al[28] conducted a prospective study involving 41 former preterm infants undergoing both minor procedures as well as major neurosurgical and thoracic procedures. Narcotics and barbiturates were given to some of those babies. Eighteen infants, all of whom were less than 41 weeks postconceptual age, had postoperative apnea or required postoperative mechanical ventilation. None of the infants greater than 46 weeks postconceptual age developed prolonged postoperative apnea. These authors concluded that infants younger than 46 weeks postconceptual age are at risk for postoperative apnea and, therefore, should not undergo outpatient surgery. They should be hospitalized and monitored for 24 hours following surgery.

In 1986, we published a prospective study using pneumography to determine the incidence of postoperative apnea and PB in infants undergoing general anesthesia for inguinal herniorrhaphy in the first year of life.[43] Our goal was to identify those infants who may develop respiratory problems if they are sent home following hernia repair. Respiratory difficulties were detected using impedance pneumography, which measures changes in impedance or resistance in the chest as respiration occurs. The monitor used in this study was Healthdyne 16000 (Healthdyne, Inc., Marietta, GA). The electrocardiographic signal (ECG) is detected and amplified, and the patient's heart rate is determined. The monitor uses standard skin electrodes as transducers for detecting both the ECG and impedance changes. Recorded data were scanned and the pneumogram analyzed by a pulmonologist for evidence of apnea, PB, and bradycardia.

Brief apnea was defined as a respiratory pause of less than 15 seconds not associated with bradycardia. Prolonged apnea was a respiratory pause of greater than or equal to 15 seconds, or less than 15 seconds if accompanied by bradycardia. PB was three or more periods of apnea of 3 to 15 seconds' duration, separated by less than 20 seconds of normal respiration. The magnitude of PB was interpreted by relating its duration to the total sleep time. To report the amount of PB, the duration of all such episodes (in minutes) was totaled. The total minutes of PB was then divided by the total sleep time (minutes) in the recording to determine the percentage of PB. A PB of less than 1% of the recording was considered normal. Bradycardia was a heart rate of less than 100 beats per minute for at least 5 seconds.

Eighty-six infants, 38 of whom were premature and 48 of whom were full term, were studied. Seven of the 48 full-term infants were less than or equal to 44 weeks postconceptual age. None of the full-term infants had a preoperative history of apnea or any other risk factor, and none developed postoperative prolonged apnea or PB (Table 1). Twenty-two of the 38 premature infants were less than or equal to 44 weeks postconceptual age at the time of surgery. Although 12 had a preoperative history of apnea, none showed preoperative or postoperative prolonged apnea or PB on pneumography. Of the 22 preterm infants who were less than or equal to 44 weeks postconceptual age at the time of surgery, 18 had a history of apnea. None experienced preoperative prolonged apnea or PB, and there were no episodes of postoperative prolonged apnea in this group. PB was noted in 14 former preterm infants with postconceptual ages of less than or equal to 44 weeks compared with none of those with a postconceptual age of greater than 44 weeks ($P < 0.001$, Fisher's exact test). Two of these 14 patients showed PB as late as 5 hours postoperatively (Fig. 1). None of the patients in this study required endotracheal intubation or controlled ventilation postoperatively.

We concluded that outpatient herniorrhaphy can be safely performed in infants greater than or equal to 44 weeks postconceptual age who do not have major respiratory, cardiac, neurologic, endocrine, or metabolic diseases. Preterm infants less than 44 weeks postconceptual age, by contrast, are at risk for developing postoperative ventilatory dysfunction. We suggested delaying nonessential surgery for such infants. When surgery cannot be delayed, we recommended that those infants be admitted to the hospital and monitored with an apnea monitor for at least 12 hours after surgery.

In another prospective study using pneumography and published 1 year later, Kurth and coworkers[26] reported a 37% incidence of prolonged apnea following anesthesia in a group of former preterm infants whose postconceptual ages ranged from 32 to 55 weeks. The initial episode of apnea occurred as late as 12 hours following anesthesia. However, some of the infants in the study by Kurth et al had more complicated medical histories than did those in our study; infants with a history of necrotizing enterocolitis and others undergoing placement of ventriculo-peritoneal shunts were included. Kurth et al concluded that former preterm infants less than 60 weeks postconceptual age should be monitored for at least 12 hours postoperatively.

This summary emphasizes the difficulty of interpreting and objectively comparing much of the existing data. Many of the data are derived from retrospective

Table 1. *Comparison of Age, Incidence of Apnea, Periodic Breathing, and Postoperative Ventilation in Groups 1 and 2*

	GROUP 1: PREMATURE INFANTS (GESTATIONAL AGE ≤37 weeks, n = 38)		GROUP 2: FULL-TERM INFANTS (GESTATIONAL AGE >37 weeks; n = 48)	
Conceptual age (wk, range)	≤44 (34–44)	>44 (45–77)	≤44 (41–44)	>44 (46–88)
Gestational age range (wk)	26–37	26–36	38–40	38–42
Number of patients	22	16	7	41
With history of apnea	18	12	0	0
Postoperative PB	14*	0	0	0
Postoperative intubation or ventilation	0	0	0	0

*$P < 0.001$, Fisher's exact test.

From Welborn LG, Ramirez N, Oh TH, et al: Postanesthetic apnea and periodic breathing in infants. Anesthesiology 65:656–661, 1986; with permission.

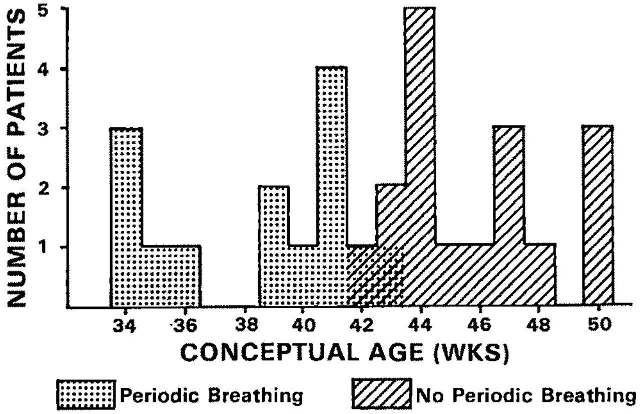

Figure 1. Distribution of conceptual age, number of patients, and incidence of postoperative periodic breathing. (*From* Welborn LG, Ramirez N, Oh TH, et al: Postanesthetic apnea and periodic breathing in infants. Anesthesiology 65:656–661, 1986; with permission.)

reviews of complications or from patients with preexisting disease who underwent complex surgical procedures. The development of prolonged apnea in preterm infants may be influenced by a host of other factors, including hypoglycemia, hypoxia, hyperoxia, sepsis, anemia, hypocalcemia, and environmental temperature changes.[34] This alone makes it difficult to interpret clearly the results of studies aimed at determining the effects of surgery and anesthesia on apnea and PB. Moreover, institutional differences regarding patient selection, care of the preterm infant, assignment of gestational age, type of surgery, type of anesthetic management, number of patients studied, and the method and duration of recording and monitoring apnea may also influence study results and conclusions. Finally, the total number of cases reported to date is quite small, standing at less than 200.

In spite of their limitations, these studies do enable one to formulate certain basic guidelines. Infants with a history of prematurity must be observed very carefully for episodes of postoperative apnea and bradycardia. The age at which the preterm infant no longer presents an increased risk must be determined on a case-by-case basis, depending on his or her growth and development and whether other medical conditions exist.

The significance of apneic episodes that are long enough to trigger a preset alarm limit or to result in bradycardia, but self-correct before cardiorespiratory arrest develops, is unknown. Deleterious hypoxic-ischemic effects on the brain may result from these episodes. A relationship of so-called insignificant apneic episodes to sudden infant death syndrome has also been suggested.[24, 36]

The possibility of life-threatening postoperative apnea and PB in the former preterm infant can be minimized by (1) deferring elective operations until the infant is greater than 44 to 46 weeks postconceptual age, if possible[28, 37, 43]; and (2) monitoring postoperative respirations and ECG in infants less than 44 weeks postconceptual age.

Having drawn certain general guidelines for the management of former preterm infants requiring surgery, we now turn to some more specialized considerations concerning this patient population. We discuss three areas: (1) the perioperative use of caffeine; (2) the use of spinal versus general anesthesia; and (3) anemia as a complicating factor in apnea and PB.

PERIOPERATIVE USE OF CAFFEINE

The methylated xanthines, theophylline and caffeine, are widely used as respiratory stimulants in preterm infants and have gained acceptance in the management of neonatal apnea.

Kuzemko and Paala[27] reported in 1973 that aminophylline significantly decreased the frequency of apneic episodes in newborns. Several other authors subsequently reported successful treatment of neonatal apnea with various theophylline preparations. Aranda and colleagues[2, 3] described similar findings with caffeine. The mechanism underlying the respirogenic effect of caffeine and other methylxanthines is not well established. It has been suggested that they increase the sensitivity of the medullary respiratory center to CO_2, since minute ventilation is increased.

In 1978 Bory et al[10] reported that theophylline is biotransformed to caffeine by premature infants and noted that a significant part of the respirogenic effect of theophylline may be attributed to caffeine. Theophylline undergoes extensive demethylation and oxidation in adults and children.[7] The demethylation and oxidation pathways, however, are immature in neonates, who tend to methylate theophylline to produce caffeine.[11] Although caffeine and theophylline share several pharmacologic actions of therapeutic interest, the former is a more potent CNS and respiratory stimulant and possesses fewer cardiac side effects than the latter.[32] Caffeine has a greater therapeutic index, is easier to administer, and has fewer peripheral effects than theophylline. In addition, it is associated with a more stable plasma concentration and therefore requires less therapeutic drug-level monitoring than does theophylline.[6]

Aranda and coworkers[4] have shown that caffeine concentrations as low as 3 to 5 mg/L can eliminate apneic spells in neonates. Plasma concentrations of 8 to 20 mg/L, however, are required for an optimal response. No toxicity has been observed with concentrations as high as 50 mg/L. Theophylline, by contrast, may cause cardiovascular side effects at plasma concentrations as low as 13 mg/L.

The effectiveness of the methylxanthines in reducing apneic episodes in infants may be reinforced by their elimination half-lives. The elimination rate of all methylxanthines is significantly decreased in the newborn infant. In adults, the half-lives of caffeine and theophylline are 6 hours[4] and 9 hours,[16] respectively; in newborns, the half-lives are prolonged (caffeine, 37–231 hours; theophylline, 12–64 hours). The half-life of caffeine decreases with age and reaches adult values by about 4 months of age.[4]

To examine the possible efficacy of caffeine in the prevention of apnea following anesthesia and surgery in former preterm infants, we designed a prospective, double-blind, randomized study that involved 20 otherwise healthy preterm infants born at less than or equal to 37 weeks gestational age.[44] All were undergoing general anesthesia for inguinal hernia repair and were less than or equal to 44 weeks postconceptual age at the time of surgery. Infants with preexisting cardiac, neurologic, or metabolic diseases, as well as those already receiving methlyxanthines, were excluded. Administration of a caffeine base, 5 mg/kg IV, given slowly immediately following the induction of anesthesia in a single dose, significantly reduced the incidence of prolonged postoperative apnea over that observed in the control group; however, it did not abolish all types of ventilatory dysfunction (Tables 2 and 3).

Although the dose of caffeine that we selected (5 mg/kg) has been shown to be effective in other studies,[40] the resultant caffeine concentration (5–8.6 mg/L) was at the low end of the ideal therapeutic range (8–20 mg/L).[5]

Therefore, we conducted a follow-up prospective, double-blind, randomized study to examine the efficacy of a higher dose of IV caffeine in the control of all

Table 2. *Perioperative Data of Study Patients*

	GROUP 1: CAFFEINE (n = 9)	GROUP 2: CONTROLS (n = 11)
Gestational age (wk)		
Mean ± SD	29.8 ± 3	31.6 ± 3
Range	25–35	26–36
Conceptual age (wk)		
Mean ± SD	40.6 ± 2	40.6 ± 2
Range	38–44	35–44
History of preoperative apnea	8 (89%)*	5 (45%)

*$P < 0.001$, Fisher's exact test.

From Welborn LG, De Soto H, Hannallah RS, et al: The use of caffeine in the control of postanesthetic apnea in former premature infants. Anesthesiology 68:796–798, 1988; with permission.

types of postoperative apnea in a population of former preterm infants identical to the first group.[5]

Thirty-two former preterm infants (≤ 44 weeks postconceptual age) undergoing inguinal hernia repair were studied. General inhalational anesthesia with neuromuscular blockade was used. No barbiturates or opioids were administered. Infants were randomly divided into two groups: group 1 received a caffeine base, 10 mg/kg IV, immediately after induction of anesthesia, and group 2 received IV saline (Tables 4 and 5). Respiratory pattern, heart rate, and hemoglobin oxygen saturation (SpO_2) were monitored using impedance pneumography and a pulse oximeter for at least 12 hours postoperatively. A pulmonologist who was unaware of the group assignments analyzed tracings for evidence of apnea, PB, and bradycardia. None of the patients who received caffeine developed postoperative prolonged apnea, PB, or bradycardia, and none had a postoperative SpO_2 of less than 90%, the predetermined cut-off point for desaturation. In the control group, 13 (81%) developed prolonged apnea 4 to 6 hours postoperatively. Fifty per cent of these infants had an SpO_2 of less than 90% at the time.

We concluded that a caffeine base of 10 mg/kg IV completely eliminated brief and prolonged apnea in this group of infants. The caffeine concentration achieved (15–19 mg/L) with this dose was well within the recommended therapeutic range for this drug and required a single IV administration. We recommend the use of caffeine base of 10 mg/kg in addition to monitoring for apnea and bradycardia in all infants at risk for postoperative apnea following general anesthesia.

Table 3. *Incidence of Postoperative Apnea and Periodic Breathing*

	GROUP 1: CAFFEINE (n = 9)	GROUP 2: CONTROLS (n = 11)
Postoperative prolonged apnea with bradycardia	None	8 (73%)*
Postoperative PB > 1%	None	2 (18%)
Postoperative apnea < 15 seconds	8 (89%)	1 (9%)
Postoperative intubation or ventilation	None	None
Postoperative caffeine level (mg/L, range)	5–8.6	0

*$P < 0.002$, Fisher's exact test.

From Welborn LG, DeSoto H, Hannallah RS, et al: The use of caffeine in the control of postanesthetic apnea in former premature infants. Anesthesiology 68:796–798, 1988; with permission.

Table 4. *Perioperative Data of Study Patients (n = 32)*

	GROUP 1: CAFFEINE (n = 16)	GROUP 2: CONTROLS (n = 16)
Gestational age (wk)		
Mean	30.0	30.4
Range	24–35	25–36
Conceptual age (wk)		
Mean	40.9	40.5
Range	37–44	37–44
History of preoperative apnea	10 (63%)	8 (50%)

From Welborn LG, Hannallah RS, Fink R, et al: High-dose caffeine suppresses postoperative apnea in former preterm infants. Anesthesiology 71:347–349, 1989; with permission.

Caffeine Preparations

Caffeine base is sparingly soluble in water. Various synthetic mixtures of caffeine have been prepared to increase its solubility. The only commercial preparation available for IV use is the caffeine sodium benzoate. However, this preparation is not recommended for use in infants because the sodium benzoate component produces kernicterus in neonates by uncoupling albumin-bilirubin binding.

Caffeine citrate is available in powder form only. Twenty mg/kg of the caffeine citrate or benzoate is equivalent to 10 mg/kg of the caffeine base. A major disadvantage is the lack of a readily available commercial preparation of the caffeine base for IV use in neonates. Caffeine base can be prepared in any hospital pharmacy from the caffeine citrate powder.

SPINAL VERSUS GENERAL ANESTHESIA

Several authors have reported of the use of spinal anesthesia in former preterm infants. Abajian et al[1] in 1984 reported a retrospective study of 36 premature infants undergoing a variety of operative procedures under spinal anesthesia. Thirty-one blocks were successful after the first attempt; five required a second attempt. Six patients who had successful spinal anesthetics required IV narcotic or nitrous oxide supplementation. There were no episodes of hypotension or bradycardia, nor were there any intraoperative or postoperative complications. Harnik et al[18] studied 20 infants who underwent 21 inguinal hernia repairs under spinal anesthesia. Eleven

Table 5. *Incidence of Postoperative Apnea Periodic Breathing and Desaturation*

	GROUP 1: CAFFEINE (n = 16)	GROUP 2: CONTROLS (n = 16)
Postoperative prolonged apnea with bradycardia	None	13 (81%)*
Postoperative PB >1%	None	4 (25%)
Postoperative desaturation < 90%	None	8 (50%)*
Postoperative intubation or ventilation	None	None
Postoperative caffeine level (mg/L, range)	15–19	0

*$P < 0.05$, Fisher's exact test.

From Welborn LG, Hannallah RS, Fink R, et al: High-dose caffeine suppresses postoperative apnea in former preterm infants. Anesthesiology 71:347–349, 1989; with permission.

of the infants in this prospective study were less than 44 weeks postconceptual age, and eight weighed less than 2500 g. Spinal anesthesia was supplemented with general anesthesia, IV ketamine, or local anesthesia in several patients. The sole reported intraoperative complication was apnea and bradycardia, which developed in one patient following injection of the tetracaine; that infant had a history of frequent apnea before surgery. Postoperative apnea developed in one patient 8 hours after the procedure when the patient became hypothermic (temperature, 34.2°C). No child demonstrated cardiovascular instability. The authors concluded that subarachnoid blockade was a satisfactory alternative to general anesthesia for selected preterm infants and suggested that it may avoid the postoperative respiratory complications associated with general anesthesia.

Although these reports on the use of spinal anesthesia in former preterm infants have been published, none of the studies prospectively compared spinal and general anesthesia in a controlled, randomized manner with the use of postoperative pneumography.

Therefore, we performed a prospective, double-blind study using pneumography to compare the effects of spinal and general anesthesia on the incidence of postoperative apnea, bradycardia, and PB in 36 otherwise healthy former preterm infants undergoing inguinal hernia repair.[46] All were less than or equal to 51 weeks postconceptual age at the time of surgery. Patients were randomly divided into three groups: group 1 patients received general inhalational anesthesia with neuromuscular blockade, and group 2 patients received spinal anesthesia using 1% tetracaine, 0.4 to 0.6 mg/kg^{-1}, in conjunction with an equal volume of 10% dextrose and 0.02 mL epinephrine, 1:1000 (Tables 6 and 7). Infants entering group 2 during the earlier part of the study also received adjunct sedation with ketamine, 1 to 2 mg/kg^{-1} intramuscularly, before placement of the spinal anesthetic (group 2A). Infants entering group 2 at a later date did not receive sedation (group 2B). Respiratory pattern and heart rate were continuously monitored using impedance pneumography for at least 12 hours postoperatively. Tracings were analyzed for evidence of apnea, PB, and bradycardia by a pulmonologist unaware of group assignment.

None of the patients who received spinal anesthesia, without ketamine sedation, developed postoperative prolonged apnea, PB, or bradycardia. Eight of nine infants who received spinal anesthesia and adjunctive intraoperative sedation with ketamine developed prolonged apnea with bradycardia. Two of these eight infants had no prior history of apnea. Only 5 of the 16 patients who received general anesthesia developed prolonged apnea with bradycardia. Two of these five infants had no prior history of apnea. We concluded that unsupplemented spinal anesthesia appears to be better tolerated by otherwise healthy former preterm infants than either general anesthesia or spinal anesthesia with ketamine sedation.

Table 6. *Perioperative Data of Study Patients (n = 36)*

	GROUP 1: GENERAL (n = 16)	GROUP 2A: SPINAL + K (n = 9)	GROUP 2B: SPINAL (n = 11)
Gestational age (wk)			
Mean	31.8	31.4	31.3
Range	25–36	28–36	26–35
Conceptual age (wk)			
Mean	43.3	41.2	40.5
Range	38–51	36–46	35–45
History of preoperative apnea	6	6	3

From Welborn LG, Rice LJ, Hannallah RS: Postoperative apnea in former preterm infants: Prospective comparison of spinal cord general anesthesia. Anesthesiology 72:838–842, 1990; with permission.

Table 7. *Incidence of Postoperative Apnea and Periodic Breathing*

	GROUP 1: GENERAL (n = 16)	GROUP 2A: SPINAL + K (n = 9)	GROUP 2B: SPINAL (n = 11)
Prolonged apnea with bradycardia*	5 (31%)	8 (89%)	0
PB >1%	1	2	0
Intubation or ventilation	0	0	0

Fisher's exact test: $^*P < 0.015$ (group 1 versus 2A); $P < 0.0001$ (group 2A versus 2B); $P < 0.06$ (group 1 versus 2B).

From Welborn LG, Rice LJ, Hannallah RS: Postoperative apnea in former preterm infants: Prospective comparison of spinal and general anesthesia. Anesthesiology 72:838–842, 1990; with permission.

ANEMIA AND PERIOPERATIVE RISK

As the relationship between postconceptual age and operative risk becomes clearer, we may focus attention on other factors that place former preterm infants at higher risk for respiratory and cardiac complications. Among these is anemia, which may play a role in apnea during the neonatal period.[23]

In the human fetus, HbF (α2, α2), constitutes the major hemoglobin (Hb) fraction. It reaches a peak of 95% at 10 weeks gestation, remains at this high level until 30 weeks, and then declines to 80% at term; most of the remaining Hb is HbA (α2, β2). After birth, HbF gradually disappears; constituting 50% of the total Hb at 1 to 2 months and 5% at 6 months of age.[31] Infants born prematurely have more HbF than term infants and smaller iron stores. As a result, the decrease in Hb concentration in preterm infants after birth exceeds that in term infants.[3, 29, 33, 39] Hb concentrations reach their lowest levels at 1 to 3 months of age, with values as low as 7 to 8 g/dL in preterm infants.[39] Erythropoiesis is active at birth and is reflected by high Hb concentrations and reticulocyte counts commonly above 5% and occasional nucleated RBCs. After the first week of life, away from the hypoxic intrauterine environment, the premature baby enters a stage of inactive red cell production; the reticulocyte counts fall to 2% or less, and the Hb concentration decreases. As the Hb concentration falls below 10 g/dL, there is a stimulus to erythropoiesis, and reticulocytes increase to between 5% and 15% over a 2-week period, followed by correction of anemia.[35, 48]

This phenomenon, which is relatively benign and self-limiting has been termed the "physiologic" anemia of prematurity. It has little apparent effect on the infant's overall well-being.[33] However, RBC transfusions have been shown to decrease the incidence of apnea and PB in premature infants.[15, 21, 22, 25] Blood transfusion, therefore, has been recommended for some infants who present with symptoms and signs such as apnea, cyanosis with feeding, diminished activity, and poor weight gain.[42] In contrast, others have found no clinical benefit from RBC transfusion.[9, 22, 25, 42]

In addition to the low Hb concentration in the first 3 months after birth, the high Hb-O_2 affinity of the preterm infant's blood may impair the release of O_2 to the tissues.[14, 29, 38] If the decrease in Hb concentration were an isolated phenomenon, it would diminish the availability of O_2 to the tissues. However, this effect is offset in part by a progressive rightward shift of the Hb-O_2 equilibrium curve that permits more O_2 to be extracted from saturated Hb. The rightward shift or increase in the P50 is due to an increase in the proportion of adult Hb relative to HbF, as well as to an increase in the concentration of 2,3 diphosphoglycerate (2,3 DPG).[14, 41]

Though specific postoperative complications have been identified in the former preterm infant,[17, 26, 28, 37, 43] it is not known whether anemia and decreased oxygen-carrying capacity contribute to the frequency of these complications. The definition of anemia in preterm infants is not precise, and the need for preoperative correction of anemia that may require blood transfusion in these infants when they are exposed to the stress of anesthesia and surgery has not been studied in a controlled, prospective manner.

To address these concerns, we conducted a prospective study to evaluate whether a relationship exists between preoperative hematocrit and the incidence of postoperative apnea, PB, and bradycardia, and to evaluate other factors that may affect oxygen availability in preterm infants.[47] Twenty-four preterm infants undergoing inguinal hernia repair, all of whom were less than 60 weeks postconceptual age at the time of operation, were studied. Hb and hematocrit (Hct) concentrations were measured preoperatively. A preoperative Hct of at least 25% was required for study participation. General endotracheal inhalational anesthesia, supplemented with neuromuscular blockade and controlled ventilation, was used. No barbiturates or opioids were administered. Following the induction of anesthesia, reticulocyte count, percent fetal hemoglobin (HbF%), 2,3-DPG, and adenosine triphosphate levels were measured. Respiratory pattern and heart rate were recorded using impedance pneumography for at least 12 hours postoperatively. Tracings were analyzed for apnea, PB, and bradycardia by a pulmonologist who was unaware of the hematologic profile of the infant.

Nineteen infants had an Hct greater than or equal to 30% (group 1), and five infants had an Hct less than 30% (group 2). The reticulocyte and HbF levels of infants in group 2 were significantly higher than those of infants in group 1; however, the adenosine triphosphate and 2,3 DPG concentrations of infants in group 2 were lower than those of infants in group 1. Infants in group 2 showed a significantly higher incidence of postoperative prolonged apnea than those in group 1. Of the four infants in group 1 who developed postoperative prolonged apnea, only one had a prior history of apnea; by contrast, four of the five infants in group 2 who developed postoperative prolonged apnea or bradycardia had no prior history of apnea (Table 8).

Table 8. *Comparison of Age, Hematologic Profile, History of Apnea, and Postoperative Complications in the Two Study Groups*

	GROUP 1: HCT ≥ 30% (n = 19)	GROUP 2: HCT < 30% (n = 5)	*P* VALUE
Gestational age (wk)			
Mean ± SD	33.5 ± 2.7	32.4 ± 3.2	>0.1*
Range	28–36	28–36	
Postconceptual age (wk)			
Mean ± SD	45.5 ± 4.6	43.6 ± 5.5	>0.1*
Range	40–54	34–51	
History of apnea	4 (21%)	1 (20%)	>0.99†
Hematologic profile			
Hematocrit % (range)	32.7–39.1	27.6–29.7	
Reticulocytes % (mean ± SD)	2.32 ± 1.34	4.42 ± 2.49	<0.05*
HbF % (mean ± SD)	36.7 ± 15.0	61.2 ± 33.8	<0.03‡
ATP (μm/dL, mean ± SD)	50.8 ± 5.6	43.0 ± 3.3	<0.008‡
2,3-DPG (μm/mL, mean ± SD)	1.55 ± 0.28	1.27 ± 0.21	>0.07‡
Postoperative complications			
Brief apnea	0	0	
PB > 1%	0	1 (20%)	>0.2†
Prolonged apnea	4 (21%)	4 (80%)	<0.03†
Bradycardia	0	1 (20%)	>0.2†

*Mann-Whitney test.

†Fisher's exact test.

‡Two sample *t*-test.

From Welborn LG, Hannallah RS, Luban NLC: Anemia and postoperative apnea in former preterm infants. Anesthesiology 74:1003–1006, 1991; with permission.

We concluded that anemia in former preterm infants may be associated with an increased incidence of postoperative apnea. Many of the anemic infants had a high percentage of HbF and a low concentration of 2,3-DPG, both of which shift the Hb-O_2 equilibrium curve to the left and decrease the amount of oxygen available to the tissues. Red cell transfusions, however, have many potential complications and cannot be recommended or justified for the correction of an otherwise medically treatable condition. Therefore, it may be preferable to delay elective surgery until the Hct is above 30% by supplementing the feeds with iron. However, when surgery cannot be deferred, anemic infants must be observed and monitored very carefully in the postoperative period.

SUMMARY

Former preterm infants less than 44 weeks postconceptual age are at increased risk for developing postoperative apnea and PB. When surgery cannot be deferred until the infant is developmentally more mature, certain measures should be taken to minimize the risk of ventilatory dysfunction. First, all infants should be admitted to the hospital and monitored for apnea and bradycardia for at least 12 hours after surgery. Outpatient surgery is not advisable for infants less than 44 weeks postconceptual age. Second, we recommend the use of IV caffeine base of 10 mg/kg in all infants at risk for postoperative apnea following general anesthesia. Preliminary results of a small number of patients indicate that spinal anesthesia without sedation is associated with less apnea than is general anesthesia or spinal anesthesia with ketamine sedation, and this option warrants further consideration. Infants with anemia of prematurity, generally a benign condition, are at increased risk for developing postoperative apnea. Therefore, it is preferable to delay elective surgery and supplement the feeds with iron until the Hct is above 30%. When surgery cannot be deferred, anemic infants must be observed and monitored carefully in the postoperative period.

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Congenital Diaphragmatic Hernia

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HISTORICAL OVERVIEW

In 1848, Bochdalek, who was Professor of Anatomy at the University of Prague, first described the classical posterolateral diaphragmatic defect that bears his name. However, it was not until 1929 that the first attempt at repair of congenital diaphragmatic hernia (CDH) in infancy was documented.[26] Successful surgical treatment in children was rare until 1940 when Ladd and Gross[45] reported 16 cases with 9 survivors, including a neonate operated on within the first 48 hours of life. In 1946, Gross[28] reported seven successful repairs in seven children, one of whom was a newborn infant less than 24 hours of age. However, all of the other children in his series presented outside the first 24 hours of life and most did not in fact have the classical Bochdalek's defect. It is noteworthy, however, that his survival rate was 100%, a figure that no other subsequent series has been able to approach. It must of course be recognized that in this era, the law of natural selection worked considerably in the surgeon's favor when it came to reporting survival as the most severely asphyxiated infants expired immediately after birth and were never referred to a pediatric surgical center for treatment. In the meantime, the past 30 years has seen many major advances in anesthesia, surgery, and intensive care in the treatment of newborn infants. Despite this, we have been unable to make a significant impact on the high mortality rates seen in CDH. In Gross's day this had seemed a relatively straightforward problem of a defect in the hemidiaphragm allowing for migration of abdominal contents into the hemithorax, with compression and failure of development of the lung on that side. The self-evident solution was a surgical repair of the defect and the only factor that precluded a successful outcome was the fact that this was major surgery being undertaken on sick hypoxic newborns. It has taken us 40 years to understand that this is far from a surgical problem with a surgical solution, and that the major factor that determines outcome is the underdevelopment of the pulmonary parenchyma and the pulmonary vascular bed. CDH in many centers is no longer considered to be a neonatal surgical emergency and much greater emphasis is now being placed on the respiratory management before surgical repair is contemplated.

This review then encompasses a brief outline of the embryology and epidemiology of CDH and discusses how the current approach to management has evolved over the past 40 years into our understanding of the major causes of mortality. Finally, a scheme of management is described that encompasses some of

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the more innovative approaches in the management of this frustrating yet intriguing anomaly.

EMBRYOLOGY AND EPIDEMIOLOGY

Until relatively recently, it has been thought that the diaphragm develops embryologically from an ingrowth of tissue that separates the abdomen from the thorax and is composed of three parts: the transverse septum (ventral), the pleuroperitoneal membrane (lateral), and the tissues of the mediastinum (medi-odorsal). It is the failure of the pleuroperitoneal membrane to form properly that causes the classical Bochdalek diaphragmatic hernia. A different concept of diaphragmatic development has been proposed by Iritani.[40] In an animal model, he has shown that the use of the drug Nitrofen (2.4-dichloro-phenyl-p-nitrophenyl ether) during gestation leads to the failure of development of the left lung and produces a left diaphragmatic hernia. He found that there was a plate of mesenchymal tissue lying dorsal to the liver where growth was inhibited by the drug. He called the region "the post hepatic mesenchymal plate." The interesting speculation arising from this study was whether CDH is secondary to the failure of normal lung development rather than the cause of it.

The incidence of CDH was thought to be between 1 in 5000 to 10,000 live births.[32] However, more recent studies by Puri and Gorman[55, 56] from a large neonatal center with 100% autopsy rate for still births and neonatal deaths showed that the true incidence was 1 in 2200 births. Polyhydramnios is commonly associated with CDH. In a series of 94 infants in which the anomaly was diagnosed by prenatal ultrasound, polyhydramnios was present in 76% of pregnancies that resulted in the birth of an infant with CDH and was associated with only an 11% survival.[1] Defects are more common on the left side, occurring in 80% of cases of the Bochdalek form of CDH. Although classically CDH has a sporadic distribution, there is a rare familial form of CDH[19, 52, 66] that is thought to be an autosomal recessive variant.[39] There is also an increased incidence of associated anomalies that has been reported to be between 40% and 50% in two large series.[5, 20] In the series by Puri and Gorman,[56] they found that there was a 100% incidence of lethal anomalies in infants with CDH who were stillborn. The most common lethal anomalies are chromosomal and cardiac defects. With the increasing use of prenatal and postnatal echocardiography, it has become clear that the incidence of severe congenital cardiac defects is higher than was originally thought. Azdick et al[3] found a 16% incidence of associated lethal anomalies based on prenatal diagnosis. Greenwood et al[27] in a retrospective review found 23% of infants with either Bochdalek's or Morgagni's defects had cardiac abnormalities. However, in a recent review of 143 cases of CDH from this institution, only 7% of infants had major cardiac defects apart from the standard findings of patent foramen ovale and ductus arteriosus. The most common lethal chromosomal abnormalities seen in CDH are trisomy 13 and trisomy 18.

PATHOPHYSIOLOGY

Pulmonary Hypoplasia and Pulmonary Vascular Abnormalities

It is has been apparent since the first attempts at surgical repair that there are differing forms of severity of CDH. Some infants present with severe hypoxemia and hypercarbia from the time of birth, which fails to improve with either hyperventilation or surgical repair, whereas others respond well to hyperventilation with normalization of blood gases, even before the hernia is reduced and the defect closed. Berdon et al[6] attempted to differentiate between these infants when they classified CDH according to the severity of the defect by recognizing that outcome depended on the degree of pulmonary hyoplasia. Group 1 were infants with a well-developed ipsilateral and contralateral lung, frequently presented after the first 24 hours of life, who invariably survived. Group 2 infants had severe hypoplasia of both ipsilateral and contralateral lungs and the potential for survival was extremely poor. Group 3 infants had a well-developed contralateral lung associated with hypoplasia of the ipsilateral side, and although they may develop ductal shunting, the potential for survival was good. All infants with Bochdalek's defect fall into catagories 2 and 3. This classification did not take into account any of the pulmonary vascular abnormalities.

The first morphometric studies of postmortem lungs in CDH were performed by Naeye et al[51] who identified significant abnormalities in the pulmonary vascular bed. These consisted of increased amounts of smooth muscle in the small pulmonary arteries when compared with age-matched controls. At the same time, the clinical observation was made that infants who underwent repair of CDH would have a period of postoperative stability with adequate postductal PO_2 values, frequently referred to as the "honeymoon period." This would be followed by an increase in pulmonary vascular resistance, resulting in right-to-left shunting across the ductus arteriosus and significant postductal hypoxemia. For a time CDH was considered as another variant of persistent pulmonary hypertension of the newborn (PPHN) and resulted in the widespread and fairly indiscriminate use of pulmonary vasodilators such as tolazoline, nitroglycerine, nitroprusside, phentolamine, chlorpromazine, and hydralazine, in an attempt to reduce the pulmonary vascular resistance and reverse the ductal shunting.[8, 9, 15, 18, 23, 49, 62, 64, 70] Apart from many anecdotal observations that there may be a transient increase in post ductal PO_2 values with the use of tolazoline in infants with ductal shunting, there are no published controlled studies that show any improvement in mortality with the use of pulmonary vasodilator therapy. On the contrary, since none of these drugs is selective in its action on the pulmonary vascular bed, their use in the severely hypoxic infant with CDH frequently results in a drop in systemic vascular resistance, a decrease in cardiac output, and the necessity for volume expansion and inotropic support to retrieve the situation.

While there is no doubt that the pulmonary vascular bed is very abnormal in CDH, there are distinct differences in lung morphometry that separate this from the other forms of PPHN. Levin[48] was the first to point out that it is the decrease in size of the pulmonary vascular bed that is the major abnormality, and that the pulmonary hypoplasia seen in CDH represents a deficiency of both alveoli and the number of vessels per unit of lung tissue. This finding was confirmed in the morphometric study of the lungs of nine infants who died following repair of CDH performed in this institution.[12] In this study we compared the pulmonary vascular abnormalites with those found in idiopathic PPHN and normal controls. Our findings showed that although there was increased medial hypertrophy of smooth muscle in the pulmonary microvasculature and abnormal extension of muscle as far as the alveolar duct level, this was far less severe than seen in idiopathic PPHN. What was much more significant was the degree of pulmonary hypoplasia seen not only in the ipsilateral but also in the contralateral lung. The total alveolar number was less than 10% of published values for healthy newborns. Our conclusion was that there was hypoplasia both of the alveoli and the pulmonary vasculature, but that the main determinant of mortality or survival were these factors rather than a major degree of reversible pulmonary hypertension. Although this study represented infants with CDH at the worst end of the spectrum in the fact that they all had significant preductal and postductal hypoxemia and CO_2 retention, it is likely that the pulmonary vascular abnormalites are far less severe in infants who survive.

Geggel et al,[24] in a study using similar morphometric techniques, showed that there was a difference in the pulmonary vascular abnormalites in infants who had a period of postoperative stability (so-called honeymoon period) compared with infants who were in the no-honeymoon group. In the former, a cross-sectional area of the pulmonary vascular bed was diminished and the arteries were smaller with medial thickening, whereas in the latter there was abnormal muscularization of the intra-acinar arteries and failure of the perinatal increase in compliance of small preacinar arteries.

In summary, there are marked pulmonary vascular abnormalites seen in CDH that consist of the abnormal development of smooth muscle and a decrease in the number of small pulmonary vessels. However, it is unlikely that these abnormalities are the major determinants of mortality or survival, given the degree of alveolar hypoplasia that undoubtedly exists in the most severely affected infants. Those infants, who present immediately after birth with severe preductal and postductal hypoxemia associated with CO_2 retention that cannot be reduced by hyperventilation, probably represent the most severe end of the spectrum of this underdevelopment of the lung and survival is unlikely.

Defining Severity and Predicting Outcome

Given the complex mixture of pulmonary hypoplasia and pulmonary vascular abnormalities resulting in varying degrees of derangement of Pa_{O_2} and Pa_{CO_2} values, there is a need for a simple, reproducible, and accurate method for assessing the degree of severity of CDH. More recently, with the introduction of innovative techniques such as extracorporeal membrane oxygenation (ECMO) and high-frequency ventilation (HFV) into preoperative and postoperative management, it is proving more difficult to evaluate the true place of these therapies in the management of CDH because of the widely different spectrum of severity in this anomaly. Only by identifying and comparing like groups of severely asphyxiated infants who cannot be managed post repair by the conventional techniques can the newer innovative therapies be properly evaluated.

Various attempts have been made in the past to determine outcome based on either the initial blood gas or pH measurements before or after surgical repair.[14, 21, 30, 50, 60] In general, there was a consistent agreement that a pH less than 7.2 and a Pa_{CO_2} greater than 50 mm Hg were associated with a poor prognosis. Although it may seem that these data would prove useful in separating those infants in the high mortality group from those with a high probability of survival, their relevance and application are obscured by inconsistencies in the site of blood sampling between preductal and postductal sites and the different times that the measurements were taken before and after the repair. Perhaps more important still was the fact that none of these values was referenced to the most important variable, namely the ventilatory parameters used. This information is highly relevant as there are obviously considerably different implications in terms of the underlying pulmonary hypoplasia, and therefore prognosis, if high airway pressures and ventilatory rates are required to achieve normocarbia and a normal pH.

Arterial oxgenation has also been used to predict outcome in CDH. Ruff et al[60] have shown a high mortality when Pa_{O_2} is less than 60 mm Hg and the pH is less than 7.2 post repair. Both Raphaely and Downes[57] and Harrington et al[30] have used the alveolar-to-arterial oxygen difference and shown that an $A\text{-}aDO_2$ of greater than 200 to 300 mm Hg is associated with a high mortality. O'Rourke et al[54] have compared two groups of infants with CDH, one who had at least one postductal Pa_{O_2} value greater than 100 mm Hg in the first 24 hours and one in whom the Pa_{O_2} was consistently less than 100 mm Hg on an FI_{O_2} of 1.0. The latter group had a 100% mortality compared with the former of 23%. In addition, they demonstrated that the high mortality group had a more severe degree of pulmonary hypoperfusion based on pulmonary angiograms showing smaller pulmonary arteries and a greater degree of pulmonary vascular obstruction.

We have attempted to use the $PaCO_2$ as an early predictor of outcome, while at the same time measuring this against an indicator of ventilation, both in terms of ventilatory rate and airway pressure, which we have defined as the ventilation index (VI) (VI = ventilatory rate × mean airway pressure).[11] We found that this correlation of $PaCO_2$ with VI accurately predicted outcome in a series of 58 consecutive infants with CDH who presented within the first 6 hours of life; 97% of infants with a $PaCO_2$ less than 40 mm Hg survived, whereas 90% of those with CO_2 retention succumbed.[12] These $PaCO_2$ measurements were made 2 hours following surgical repair, in order to allow sufficient time for appropriate respirator adjustments to be made in an attempt to achieve optimal ventilation. We also extended this observation to the preoperative period in order to identify the high-risk group with severe hypoxia and CO_2 retention despite optimal ventilation settings, who would correspond to the group 2 infants in Berdon's classification of infants with severe bilateral pulmonary hypoplasia.[6] In our most recent series of 30 consecutive infants over a 2-year period,[10] we have found an even better correlation between outcome and $PaCO_2$/VI before surgical repair (Fig. 1). Those infants in whom normocarbia could be achieved with a VI less than 1000 had a 100% survival (zone A), whereas mortality was drastically increased with a $PaCO_2$ greater than 40 mm Hg (zone B), where only one infant with hypercarbia and a VI greater than 1000 survived, and this was only after the $PaCO_2$ was reduced with HFV. In zone C, which included infants in whom the $PaCO_2$ could only be reduced with high mean airway pressures (>20 cm H_2O) and rapid respiratory rates (>60/min), resulting in a VI greater than 1000, outcome was less predictable. There were three survivors and five deaths (38% mortality). Although we believe that infants with a VI greater than 1000 and a $PaCO_2$ greater than 40 mm Hg represent a group in whom the degree of pulmonary hypoplasia was incompatible with life using conventional treatment modalities, other centers have had survivors when ECMO support was used for infants from this group.[37, 41, 58, 68]

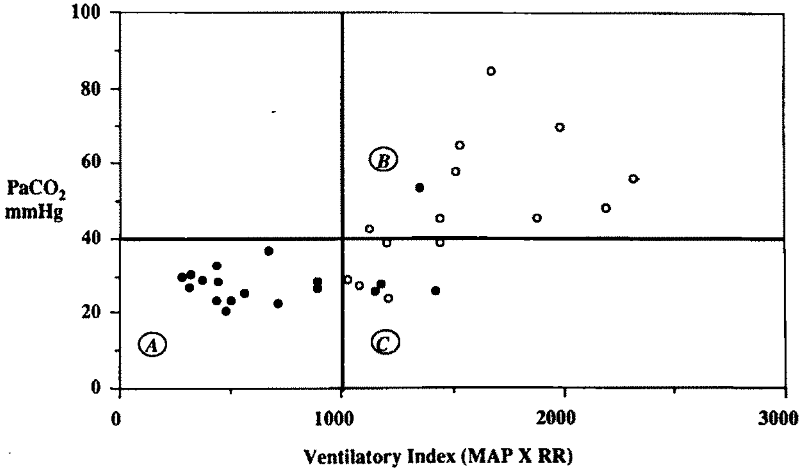

Figure 1. Correlation between outcome and $PaCO_2$ and VI. (○) Deaths; (●), survivors. (*A*) 100% survival with a VI of 1000; (*B*) drastically increased mortality with $PaCO_2$ 40 mm Hg; (*C*) less predictable outcome with mean airway pressures greater than 20 cm H_2O; and respiratory rates greater than 60 per minute. (*From* Rohn OJ: Ventilator and blood gas parameters in predicting survival in congenital diaphragmatic hernia. Pediatr Surg Int 2:236, 1987; with permission.)

Changes in Respiratory System Mechanics Following Surgery in Congenital Diaphragmatic Hernia: A Rationale for Delayed Surgical Repair

The rationale for urgent surgical repair in CDH has been that reduction of the hernia and repair of the diaphragmatic defect always improves the hypoxia and hypercarbia associated with this anomaly. This was based on the assumption that the presence of abdominal contents within the hemithorax resulted in not only compression and failure of development of the ipsilateral lung but also some compromise of the contralateral lung due to mediastinal shift. The logical answer was to reduce the hernia and close the defect in the expectation that the blood gases and lung function would improve. However, some years ago we made the empirical observation that rather than improving following repair, there was frequently a worsening of hypoxemia and hypercarbia, necessitating an increase in airway pressure and ventilator rate settings in an attempt to compensate for this deterioration. This observation prompted us to perform some measurements of respiratory mechanics before and after surgical repair to see if this worsening of blood gas values could be explained by a change in respiratory system compliance. In this study, we compared the compliance of the respiratory system before and after surgical repair and found that far from improving the total respiratory system, compliance decreased significantly after surgery, particularly in the nonsurvivors, in whom it never returned to the preoperative level.[61] Furthermore, we demonstrated that a decrease in respiratory system compliance of greater than 50% was associated with a 100% mortality. The factors that we proposed that could be responsible for this change were downward displacement of the diaphragm and distortion of the lower chest wall associated with incorporation of the internal oblique muscle in the repair of the defect and the raised intraabdominal pressure associated with replacement of intestines and organs into the abdominal cavity, where the difficult abdominal closure causes upward displacement of the diaphragm and an increase in intrathoracic pressure. The clinical significance of this change in compliance is easier to understand if it is correlated with the simultaneous change in $Pa{CO_2}$ levels (Fig. 2). In each instance, the decrease in respiratory system compliance after surgical repair is associated with an increase in arterial $P{CO_2}$ that required an alteration in ventilator settings. While in some cases an increase in ventilation pressure or rate may result in a return of the $Pa{CO_2}$ to normal, in some infants this was not possible to accomplish by changes in ventilator settings. The conclusions from this study were that far from improving, these infants were frequently worse in terms of respiratory mechanics and blood gas values after surgical repair, and the notion that compression was a major factor in the hypoxemia and hypercarbia seen before surgical repair was somewhat of an oversimplification. This in turn led us to rationalize our decision about the timing of surgical repair and to adopt a strategy of nonurgent or deferred surgery in the management of infants with CDH. Infants are no longer repaired on an emergency basis and not within the first 12 hours of life.

Following the adoption of this conservative approach, there was a gradual increase in the postnatal age at repair in our series of infants with CDH from a mean age of 8 hours (range, 3.5–16 hours) in 1983 to 38 hours (range, 14–120 hours) in 1986.[13] Since we have shown that surgery may actually worsen ventilation, there has been a significant increase in the numbers of infants who have died without having had their hernia repaired, but this has been coupled with a decrease in overall mortality in CDH, which was 58% in 1983 to 1984 and down to 50% in 1985 to 1986 (repaired and nonrepaired).[46] The overall mortality in CDH with deferred surgical repair for the past 3 years is now 43%, which includes both those treated surgically and those who could not be stabilized and died before repair. We are convinced that the concept that surgical repair in the immediate postnatal period results in improved gas exchange and is essential for survival is incorrect and may in fact increase mortality. In the severely asphyxiated infant, surgery may

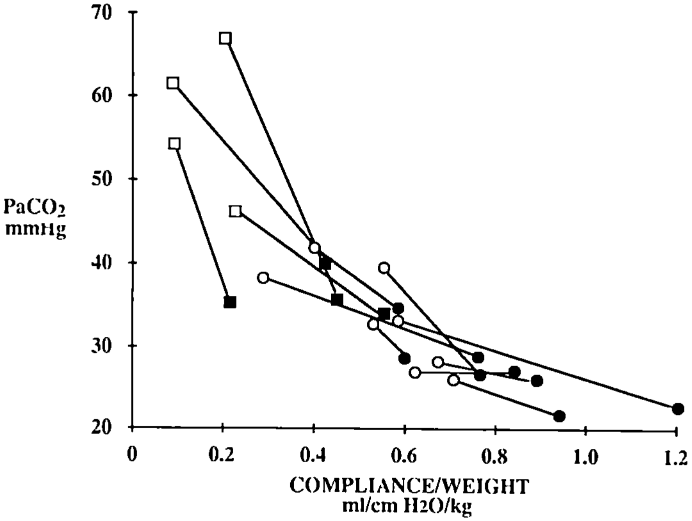

Figure 2. Correlation between compliance and Pa_{CO_2} levels. Survivors: (●) preoperative, (○) postoperative; nonsurvivors: (■) preoperative, (□) postoperative. (*From* Sokai H, Rohn DJ, Bryan AC: Congenital diaphragmatic hernia: Does surgical repair really improve respiratory mechanics. Jpn J Pediatr Surg 19:881, 1987; with permission.)

in fact result in an imbalance of transdiaphragmatic mechanical forces and worsening gas exchange, which may contribute to mortality. Efforts should be concentrated on improving ventilation and gas exchange, while surgery is deferred in the expectation that better oxygenation and CO_2 elimination will have beneficial effects on the reactive pulmonary vascular bed and thereby increase the chances of eventual survival.

CONGENITAL DIAPHRAGMATIC HERNIA: APPROACHES TO MANAGEMENT

Mechanical Ventilation

The successful ventilatory management of an infant with CDH is based on the clear understanding that there are two distinct components to the lung pathology in this anomaly, namely pulmonary hypoplasia and pulmonary vascular abnormalities, which can be influenced to varying degrees by ventilatory management. Since the classic experiments of Rudolph and Yuan,[59] which demonstrated that the pulmonary vascular bed of the newborn is exquisitely sensitive to changes in not only the Pa_{O_2} but also in pH via the arterial Pa_{CO_2}, hyperventilation has been one of the mainstays of treatment of PPHN in the newborn period. Drummond et al[22] have shown that ductal shunting in the neonate with PPHN can be readily reversed by raising the pH to greater than 7.5 and reducing the Pa_{CO_2} to less than 30 mm Hg with hyperventilation. Since the first description of pulmonary vascular abnormalities in CDH this strategy has been the first line of treatment of right-to-left shunting. It is our practice to hyperventilate these patients to maintain the pH above 7.5, supplemented with bicarbonate therapy if reduction of the Pa_{CO_2} fails to induce an alkalosis. Those infants in whom a satisfactory reduction of Pa_{CO_2} can be achieved with hyperventilation are maintained paralyzed with a Pa_{CO_2} less than 35 mm Hg for 48 hours to minimize the risk of ductal shunting, before the relaxants are discontinued and the Pa_{CO_2} is allowed to increase. If ductal shunting does occur in this category of patient, it is frequently reversible with the reinstitution of paralysis and hyperventilation, without having to resort to the use of pulmonary vasodilator therapy.

Unfortunately, by no means do all infants respond satisfactorily to hyperventilation alone because the underlying problem is more than a labile pulmonary vascular bed. Nonsurvivors with persistent hypercarbia and hypoxia who failed to respond to hyperventilation have a severe reduction in alveolar number in both lungs. In addition to the hypoplasia, the lungs of these infants are highly susceptible to futher damage due to the high positive pressures used during mechanical ventilation, hyaline membrane formation being a common finding at postmortem. Although this is widely believed to be secondary to the effects of barotrauma rather than a true deficiency of surfactant, it is worth noting that low lecithin to sphingomyelin ratios have been found in amniotic fluid taken from mothers in whom a prenatal diagnosis of CDH has been made,[7, 38] which suggests that the lungs may be immature as well as hypoplastic.

High-Frequency Ventilation

In the group of infants with CDH who cannot be managed with conventional ventilation following repair of the defect, an alternative ventilation strategy of management has been advocated, namely the use of HFV.[13, 16, 17, 43, 65] When dealing with the infant with hypoxia and CO_2 retention despite conventional ventilator settings, it has become widely accepted in neonatal practice that increasing the ventilator rate to the range of 100 to 150 per minute rather than increasing the airway pressures may improve gas exchange and result in less pulmonary barotrauma. This has been defined as high-frequency positive pressure ventilation (HFPPV) to distinguish this from other forms of HFV, where frequencies in excess of 1 per second are used together with tidal volumes considerably less than dead space ventilation.

Of the latter type there are basically two different types of HFV currently being used in neonatal practice, namely high-frequency oscillation (HFOV) and high-frequency jet ventilation. These have distinctly different modes of operation. The high-frequency oscillator is a piston within a cylinder producing a high-frequency sine wave that is applied to the airway and ventilatory rates in the range 5 to 15 Hz. On the other hand, high-frequency jet ventilation is a high-pressure gas source coupled with flow interuption that delivers small tidal volumes via a catheter in the airway at frequencies of 1 to 5 Hz.

Considerable experience has now been accumulated on both these techniques in the management of neonatal respiratory failure, principally in dealing with hypercarbia, where both systems have proved very effective in reducing Pa_{CO_2} in instances in which conventional techniques have failed. The effect on Pa_{O_2} has been less spectacular and less consistent, but most series show a significant rather than dramatic improvement in oxygenation with the switch to HFV, as measured either by a decrease in A-aDO_2 or an improvement in a-A ratio.[13, 16, 17, 43, 65]

Over the past 10 years we have used HFOV in over 50 infants with CDH either before or after surgical repair in whom severe preductal and postductal hypoxemia and hypercarbia could not be reversed despite vigorous attempts at hyperventilation (VI $>$ 1000). In each instance there has been a prompt and rapid reduction of Pa_{CO_2} to hypocarbic levels, using similar airway pressures to conventional ventilation. Although there was an initial improvement in oxygenation in the infants who were switched to HFOV, this was not sustained for more than 24 hours in most instances. Part of the explanation for this initial improvement in Pa_{O_2} may be ascribed to the immediate reversal of the respiratory acidosis with an increase in pH to greater than 7.5 and a consequent decrease in right-to-left shunting through the ductus. Although we have had relatively few survivors in this severely affected group of infants, in whom the mortality was previously 100%, we have been able to control the hypercarbia and acidosis in many instances before reduction of the hernia and closure of the defect. This has enabled us to institute a policy of delayed surgical repair rather than operate on a severely acidotic and hypoxic infant.

Previously published studies using HFV in CDH have also reported a similar gratifying reduction in Paco$_2$, but also without an improvement in outcome. Karl et al,[43] using HFOV, reported a reduction in hypercarbia and an initial increase in Pao$_2$, but the four infants did not survive. Boynton et al[17] reported only one survivor of four infants, despite a similar rapid reduction in Paco$_2$ using a combination of HFOV superimposed on conventional respiration. Boros et al,[16] on the other hand, used the high-frequency jet ventilation technique in five infants with CDH, among a group of 23 patients with various forms of neonatal respiratory failure, with similar results to the HFOV group. Finally, Tamura et al[65] have reported the successful use of HFOV for prolonged postoperative ventilatory support following repair of CDH.

Extracorporeal Membrane Oxygenation

Since the early 1980s with the introduction of ECMO for the management of respiratory failure in the newborn, there has been an increasing tendency to use this technology to support infants who deteriorate after repair of CDH.[4, 25, 29, 42, 58, 63, 68] It has been commonly assumed that the primary cause of this deterioration is due to a reactive pulmonary vascular bed with abnormally muscularized vessels and right-to-left shunting across the ductus arteriosus, and there has been an expectation that these changes might regress if the infant could be supported on ECMO. The criteria that have been used to institute ECMO in this situation are the standard criteria that are used for defining ECMO eligibility in other forms of neonatal respiratory failure and include the A-aDO$_2$, the a-A ratio, the oxygenation index, and failure to respond to maximal medical treatment.[44, 47] Langham et al,[47] in a review of the literature of outcome from ECMO support in CDH, found that the most common selection criteria used for postoperative ECMO support was "acute deterioration." This highlights that one of the major problems in evaluating this therapy is the diversity of criteria used for ECMO eligibility. However, there are now several published reports of successful ECMO support being used in a group of infants that we have previously defined as having severe pulmonary hypoplasia based on an elevated Paco$_2$ and a VI greater than 1000, although in each instance the infants were scored retrospectively.[37, 41, 58, 68] Although some centers are reporting an increased number of survivors with their use of ECMO support, it is difficult to evaluate these results since they have included both infants that have been primarily managed and repaired at the neonatal ECMO center together with infants who have been repaired at other centers and then referred for ECMO support after they deteriorate. It is worth noting that the National ECMO Registry Center data show that the worst outcome in ECMO-treated babies occurs in the CDH group, with only a 62% survival compared with over 85% for other forms of neonatal respiratory failure. O'Rourke et al,[53] in a recently published series from the Children's Hospital in Boston, have reported an overall mortality of 51% in severe CDH between 1984 and 1987 after ECMO was introduced, compared with 53% before ECMO was used. Included in these results are infants who were admitted to their center preoperatively as well as those transferred after repair. In the group of infants that was admitted preoperatively the overall mortality (ECMO plus conventional treatment) was 50%. It still remains unclear whether the widespread use of ECMO will result in a further decline of the mortality in CDH below the 45% reported in centers where ECMO is not being used. If the assumption that the major cause of mortality in CDH is pulmonary hypoplasia, then it is unlikely that sufficient alveoli will develop to sustain life over a period of ECMO support. Whether or not the more widespread use of ECMO in CDH will result in a decrease in mortality has yet to be determined. The selection criteria for the use of ECMO remain too ill-defined and in most cases where the hypoxemia is due to ductal shunting, this can be managed effectively by optimal conventional ventilation. If there is a place for ECMO support in the severe form of CDH, it would seem more logical to follow the approach, already successfully used, that ECMO support be used preoperatively to improve the oxygenation and CO_2 removal rather than postoperatively.[53, 67]

Prenatal Diagnosis and Fetal Surgery

As increasing expertise and experience is developed in the use of prenatal ultrasound, it has become possible to accurately diagnose CDH prenatally. Despite this, the diagnosis may be missed in routine prenatal ultrasound examinations unless an associated risk factor such as polyhydramnios is present. In those cases in which positive identification of a diaphragmatic hernia is made, the most common time is around the 30-week gestation mark, although there are isolated instances of a diagnosis of CDH being made at 17 weeks gestation.[1] Unfortunately, the prenatal diagnosis of CDH does not lead to increased survival, with an 80% mortality being reported in this group despite the institution of immediate attempts to resuscitate and stabilize the infant.[1] In a further study of 38 cases diagnosed by ultrasound there were no survivors where the diagnosis was made before 25 weeks gestation.[3] However, the ability to diagnose these defects before delivery has opened the possibility that the hernia could be repaired in utero relatively early in pregnancy to allow for possible normal lung development. Experience in this technique has been gained by the pioneering work of Harrison and colleagues using an animal model of CDH whereby a diaphragmatic defect is created in fetal lambs and an inflated balloon is placed into the left hemithorax producing compression and inhibiting development of the lung.[2, 31, 33, 34, 36] It has been shown experimentally that intrauterine repair of the defect results in relatively normal development of the ipsilateral lung.[2, 33]

Initial attempts at intrauterine repair in humans proved at first to be unsuccessful. In the first four fetuses that were operated on by Harrison et al there were no survivors to hospital discharge, although one infant did survive the postdelivery period.[35] More recently they have reported two surviving infants whose mothers underwent intrauterine repair.[35] However, this form of surgery is still largely experimental and does submit the pregnant mother to some degree of risk from the surgical procedure. It still remains to be seen whether fetal surgery will lead to a substantial reduction in the high mortality in CDH.

CONGENITAL DIAPHRAGMATIC HERNIA: CURRENT APPROACH TO MANAGEMENT

Our increased understanding of some of the more complex underlying problems associated with CDH over the past 10 years has led to a reorganization of the priorities and treatment. Some of the fundamentals, however, remain the same, namely the importance of stabilizing the infant in the postdelivery period and avoiding iatrogenic complications such as acute gastric distention from overenthusiastic bag and mask ventilation, contralateral pneumothorax from the use of excessive positive pressure, and the correction of acidosis and hypoglycemia in order that the neonate can be transferred to a neonatal surgical center in optimal condition. The second priority is to avoid factors that may precipitate ductal and preductal shunting, both in the preoperative and postoperative period. For over 10 years the use of hyperventilation has been a mainstay of management of PPHN in the neonatal intensive care unit. We have endeavored to adopt this approach in the preoperative and postoperative management of infants with CDH and maintain the pH above 7.5 by reducing the $Paco_2$ with conventional mechanical ventilation where possible or switching to HFOV when hypercarbia persists despite manipulations of ventilator rates and pressures. In order to minimize any increase in intrathoracic pressure, we use neuromuscular blockade with nondepolarizing muscle relaxants and sedation and analgesia by IV narcotic infusion (morphine or fentanyl). There is some published data that suggest that high doses of IV fentanyl may have selective pulmonary vasodilator properties in this situation[69] although there are no studies that show it to be superior to other narcotics.

The Timing of Surgical Repair

With the changing emphasis placed on the importance of early surgical repair in infants with CDH, many centers do not now consider that surgical repair in the first 6 hours of life is either necessary or even desirable. In our own institution, we have followed a policy of deferred surgical repair for the past 5 years, based on whether the infant has a mild degree of pulmonary hypoplasia associated with minor degrees of blood gas derangement, or whether there is severe underlying pulmonary hypoplasia associated with severe hypoxemia, hypercarbia, and acidosis. We have applied the scoring system of using the $Paco_2$ and ventilation index to decide when, or indeed if, the infant should have surgical repair (Fig. 3). Those infants with a VI of less than 1000 and a $Paco_2$ of less than 40 (group A) will have their defect repaired on the next day's operating list (within the first 12–24 hours of life), with the expectation that there would be minimal disturbance to blood gas exchange and they will do well if shunting across the ductus arteriosus can be controlled with paralysis and mild degrees of hyperventilation. Those infants who present with a VI greater than 1000 and a $Paco_2$ greater than 40 are placed on high-frequency oscillation in order to reduce their CO_2 and reverse the acidosis. They will not undergo surgery until such time as the $Paco_2$ can be maintained below normal on conventional ventilation. Attempts at repair before this will only worsen the condition. Those infants in whom a normal $Paco_2$ (<40 mm Hg) has been achieved by the use of high rates and pressures (VI > 1000, group C) will have their surgery deferred for at least 24 hours in the hope that their respiratory function will improve

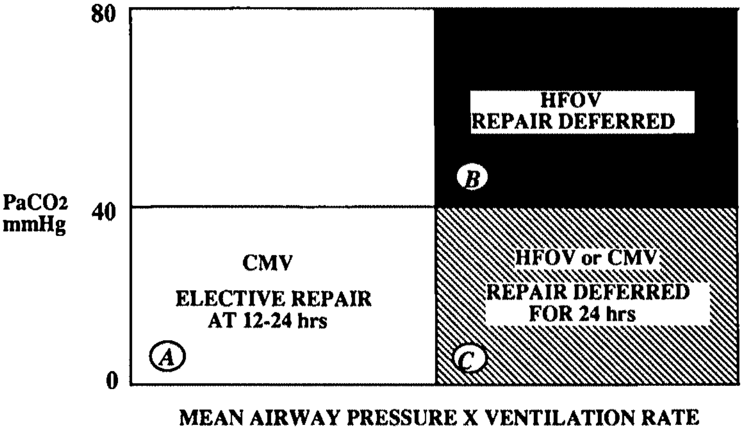
80
PaCO2 mmHg
40
0
HFOV
REPAIR DEFERRED
B
CMV
ELECTIVE REPAIR AT 12-24 hrs
A
HFOV or CMV
REPAIR DEFERRED FOR 24 hrs
C
MEAN AIRWAY PRESSURE X VENTILATION RATE

Figure 3. Outline plan for the timing of surgical repair based on a scoring system of $Paco_2$ and ventilation rate.

by manipulations of either conventional ventilation or HFV. Early surgical repair in this group of infants frequency results in an adverse effect on respiratory mechanics and a substantial increase in $Paco_2$ that cannot be compensated for by increasing ventilation. Many of these infants have a protracted course associated with substantial amounts of ventilation-induced lung injury. It has yet to be proved whether ECMO support after presentation and repair of the defect while on bypass will lessen the degree of pulmonary barotrauma and increase the number of survivors.

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Malignant Hyperthermia: Treatment and Aftercare

*John F. Ryan, MD**

INCIDENCE

Malignant hyperthermia (MH) is a relatively rare disorder that is estimated to occur in one in every 50,000 to 100,000 adult patients undergoing general anesthesia; in children its incidence is reported to be one in every 3000 to 15,000.[9, 101] The difference is more likely due to the retrospective nature of the studies and the age at which most surgery is performed. MH occurs almost exclusively during or following an anesthetic procedure, and it is more frequently reported with halothane anesthesia, especially when succinylcholine has been utilized.[64] However, it can occur with other halogenated agents, and even in their absence.[6, 36, 98]

Although deaths from high fever were a known complication of anesthesia, the initial descriptions of MH were not recognized as a separate entity until the syndrome was accurately characterized by Denborough and Lovell in 1960.[24] At that time, the mortality rate approached 90%. With increased awareness of the syndrome and symptomatic management, the mortality rate dropped to 60% in the 1970s. However, the real breakthrough in the management of MH occurred in 1979, when the specific effectiveness of dantrolene sodium was recognized in the prevention, as well as the treatment, of this syndrome.[53, 64] The cumulative benefit of intravenous dantrolene, increased awareness of MH, and improved monitoring has decreased the mortality from MH to less than 10%.

DIAGNOSIS

The goal in the successful outcome of an episode of MH is early recognition and prompt treatment. To facilitate the diagnosis of MH, the anesthesiologist must have a thorough understanding of the signs and symptoms of this syndrome and be able to differentiate MH from other hypermetabolic disorders.

Because the first systemic effect of this syndrome is increased metabolism (oxygen consumption), the cardiovascular and respiratory systems respond to this increased demand by increasing their output. Therefore, *the first signs of this syndrome are tachycardia and tachypnea.*

Although light anesthesia is often the cause of tachycardia, in a healthy child of 7 years of age, an increase from 120 to 180 beats per minute (or an increase from 70 to 120 beats per minute in an adult) is usually a sign of disease. Not all tachycardia or tachypnea is attributable to "light" anesthesia (Table 1). It is reasonable to increase the depth of anesthesia, but it is also vital immediately to rule in or out other mechanical factors (such as endobronchial intubation, hypoventilation, and a circuit problem). If these prove normal and a brief trial of deepened anesthesia fails to slow the heart rate, then a simultaneous central venous and arterial blood sample should determine the presence or absence of a hypermetabolic state. In this respect *the expired CO_2 monitor is invaluable. In hypermetabolic states, the expired CO_2 will be high, especially during MH.* In this condition, it becomes extremely difficult to bring the end-expired CO_2 level within the normal range, even with vigorous hyperventilation. In situations of airway obstruction, the recorded CO_2 levels will be elevated; however, once the defect has been corrected, end-tidal CO_2 will return rapidly to its normal value, with mild to moderate hyperventilation.

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MH can also present initially as ventricular ectopy in otherwise healthy patients; this is especially common during induction of anesthesia. If there is no airway instrumentation, hypercarbia, hypoxia, or some other stimulus to explain the arrhythmia, in addition to other myopathies (i.e., Duchenne's muscular dystrophy) MH becomes suspect. Electrocardiographic investigation must also be carried out, as well as myoglobin and creatinine phosphokinase (CPK) levels. If the electrocardiogram is normal and the CPK and myoglobin are elevated, one can make a tentative diagnosis of MH (Table 2).

DIFFERENTIAL DIAGNOSIS

In the operating room, sudden onset of high fever can be attributed to many problems. Sepsis, neurologic injury, thyroid storm,[4] metastatic carcinoid, pheochromocytoma,[21] drug reaction (monoamine oxidase inhibitor and Demerol), drug overdose (cocaine), and transfusion reaction all can be associated with high fever. At our institution, eight patients with intraoperative temperatures above 108°F were seen between 1974 and 1979. These patients all had sepsis or prior neurologic trauma. The acid-base status remained normal in all these cases. Thyroid storm has not been associated with severe acid-base abnormalities in the few anecdotal reports available. Examination of the neck may be helpful in the differential diagnosis of this entity. Muscle rigidity separates MH from thyroid storm. In patients presenting with metastatic carcinoid or pheochromocytoma, the initial symptoms resemble MH but the marked cardiovascular instability persists after dantrolene therapy.

Today, most cases of MH are aborted owing to the recognition by the anesthesiologist that a hypermetabolic episode is present or developing. The hallmark of a fulminant episode is hypermetabolism. Increased production of carbon dioxide and extraction of oxygen are easily detectable by capnography elevation and a lowered oximetric value despite adequate or increased ventilation and delivered oxygen concentration. Documentation of abnormalities is important to solidify the diagnosis as time passes and diagnostic assurance wavers. Creatinine kinase levels

Table 1. *Signs and Symptoms of Malignant Hyperthermia*

Tachycardia	Fever
Tachypnea	Hyperkalemia
Respiratory acidosis	Cyanosis
Metabolic acidosis	Prolonged coagulopathy

Table 2. *Presentation of Malignant Hyperthermia*

Masseter rigidity	Neuroleptic malignant syndrome
Succinylcholine-induced muscle rigidity	Heat stroke
Full blown in operating room	Episodic fever
Full blown in recovery room	Sudden infant death syndrome
Intraoperative fever alone	

are usually not elevated during the acute episode, but potassium levels, myoglobin determination, and thyroid studies can be useful in early aborted cases in determining the proper diagnosis.

DANTROLENE

When a full-blown episode of MH is diagnosed, *immediate aggressive therapy* is indicated. Table 3 outlines the standard treatment regimen. The keystone of this approach is dantrolene sodium (Dantrium). This drug has been shown to be effective at an intravenous (IV) dose of 2.5 mg/kg without any major adverse effect. If administered early during the episode, it reverses the biochemical changes of MH and decreases cellular metabolism.[64] If its administration is delayed for more than 24 hours, it still reverses some of the clinical signs but does not affect the mortality rate.

Although dantrolene is the key to successful outcome, the other ancillary measures are also very important (see Table 3). Active cooling, treating the associated acidosis, and correcting the electrolyte imbalance can make the difference between a borderline or completely adequate recovery.

Dantrolene has probably been responsible for the dramatic decrease in the mortality from MH since its intravenous use was introduced in the United States in 1979. The drug instructions recommend an initial dose of 1 mg/kg IV. However, a small number of patients do not respond to this dosage level. Because no major side effects occur after a large dose, we strongly suggest an initial bolus dose of 2.5 to 3.0 mg/kg IV, followed in 45 minutes by a bolus dose of 10 mg/kg if all signs and symptoms of the syndrome have not resolved.* The complete cessation of (1) tachycardia, (2) tachypnea, (3) all rigidity, (4) decreased urinary output, (5) altered consciousness, (6) blood gas abnormalities, and (7) electrolyte disturbances should be attained. If this does not occur with initial therapy, a repeated higher dose of dantrolene should be administered, or an alternate diagnosis for the problem should be sought.

Two recent experiences exemplify the reasons for this recommendation. A 19-year-old patient who developed MH was treated with dantrolene at a dosage of 1 mg/kg IV. Twelve hours postoperatively, all signs of MH were absent except tachycardia (180 beats per minute) and marked hypertension (240/150 mm Hg), despite vigorous doses of nitroprusside, nitroglycerin, and hydralazine. After IV dantrolene in a dose of 3 mg/kg, a brief improvement of the cardiovascular aberrations followed. Subsequent to 10 mg/kg of dantrolene IV, dramatic return of all parameters to normal values occurred.

The second patient developed a full-blown picture of MH, and 20 hours later was still unconscious, with marked left gastrocnemius muscle spasm. He was

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*Editorial note: Management differs among experts. Others recommend an initial bolus of 2.5 mg/kg IV followed by 1 mg/kg IV every 5 to 10 minutes until all signs and symptoms of MH resolve.

Table 3. *Standard Treatment Regimen for Malignant Hyperthermia*

Stop anesthesia and surgery immediately
Hyperventilate patient with 100% oxygen
Administer dantrolene (Dantrium) 2.5 mg/kg IV and procainamide (up to 15 mg/kg IV slowly if required for arrhythmias) as soon as possible
Initiate cooling
Correct acidosis
Secure monitoring lines: EKG, temperature, Foley catheter, arterial pressure, central venous pressure
Maintain urine output
Monitor patient until danger of subsequent episodes is past (48–72 hr)
Administer oral or IV dantrolene for 48–72 hr

receiving 1 mg/kg of dantrolene IV every 8 hours as a maintenance dose to prevent recurrence of MH; 30 minutes following IV dantrolene in a dose of 10 mg/kg, the patient was awake and the muscle spasm gone.

In our experience, the response to dantrolene takes 6 to 20 minutes. End-expired Pco_2 will begin to decrease in about 6 minutes, and monitored arterial blood gas analysis will show significant restoration toward normal in 20 minutes. The important factor is that, by 45 minutes, the patient should be completely normal. If not, intensive therapy should be pursued. Ten percent of MH patients following a full-blown episode redevelop the syndrome, so-called recrudescence. This usually occurs 4 to 8 hours after the initial episode and has been noted up to 36 hours after initial therapy. Characteristically, patients "smolder" along with modified symptoms until a triggering event ignites a renewed full-blown episode.[85] Table 4 outlines the signs and symptoms of a continuing subclinical episode of MH.

Patients with recrudescence have died owing to a change in muscle cellular permeability. Such patients require enormous fluid volume infusions to maintain intravascular volume. Muscles immediately take up this volume and swell dramatically. The two patients who developed MH in our institution in 1979 gained 24 kg in 18 hours, and 15 kg in 36 hours, respectively.

Once the initial episode has been successfully treated, patients traditionally have been given 1 mg/kg of dantrolene IV every 6 hours for 24 hours, or by mouth for an additional 48 to 72 hours. There are no data to substantiate this therapy in the absence of further evidence of an MH reaction.

Dantrolene's action has been identified as being specific for skeletal muscles.[29, 94] It does not affect neuromuscular transmission or have measurable effects on the electrically excitable surface membrane. It does, however, produce muscle weakness and may potentiate nondepolarizing neuromuscular blocking agents. Indirect evidence indicates that the site of action of dantrolene sodium is within the muscle itself and is related to the caffeine-sensitive calcium stores. It is suggested that dantrolene sodium prevents the release of calcium from the sarcoplasmic reticulum or antagonizes calcium effects at the actin-myosin-troponin-tropomyosin level, or both (Fig. 1).[40, 119] Such actions are proposed as explanations for the skeletal muscle relaxant activity of the drug observed clinically. Some unique properties of the drug include the following:

1. At doses from 5 to 15 mg/kg IV it produces a significant degree of muscle relaxation.
2. In IV doses up to 15 mg/kg it has no significant action on the cardiovascular system.
3. At IV doses up to 30 mg/kg it does not depress respiration.

Table 4. *Signs and Symptoms of Continuing Malignant Hyperthermia Episode*

Continued hyperkalemia
Residual rigidity still present
Massive fluid requirements
Oliguria proceeding to anuria

4. There is no indication of hepatic toxicity when the drug is administered IV on an acute basis.

By reducing rigidity and restoring muscle function, dantrolene normalizes all functions associated with muscle hypermetabolism in MH. One important example is the rapid reduction in serum potassium, because potassium is restored to muscle cells. This ultimately normalizes cardiac function. As cellular metabolism returns to aerobic processes and respiration normalizes, acid-base disorders are corrected. Thus, although dantrolene acts primarily on skeletal muscles, its beneficial effects are far reaching.

ANESTHESIA FOR THE PATIENT WITH SUSPECTED MALIGNANT HYPERTHERMIA

Lerman et al[69] reported that with dantrolene pretreatment, only 0.6% of biopsy-positive patients developed MH reactions after a trigger-free anesthetic for a muscle biopsy. The common practice is not to "routinely" use dantrolene preoperatively. This eliminates muscle weakness and nausea frequently associated with pretreatment in adults.[120]

When a surgical procedure is planned in a known MH-susceptible patient, pretreatment with oral or IV[38] dantrolene sodium may be administered because of a history of a severe episode of MH or the patient's or anesthesiologist's terror. The oral dose recommended is 4.8 mg/kg orally four times a day for 48 hours before anesthesia. The IV dose of dantrolene is 2.5 mg/kg.[64] This dose achieves a steady-state blood level greater than or equal to 3.0 μg/mL for approximately 6½ hours, then decreases slowly, with a half-life of 10 hours.[70] IV dantrolene pretreatment may be given immediately before induction of anesthesia. Patients have been

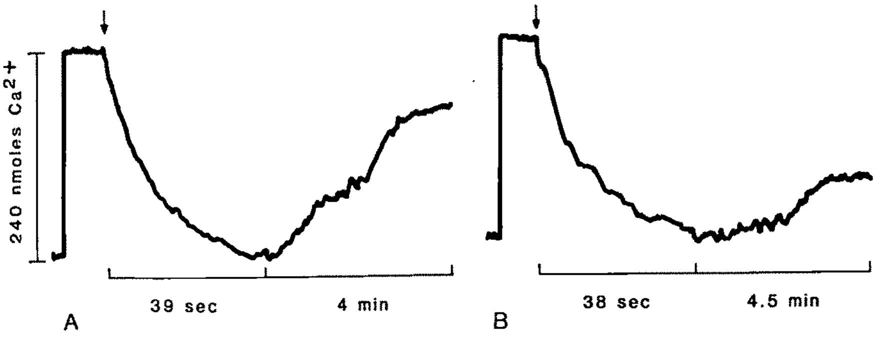

Figure 1. Dual spectrophotometric tracing captures the uptake and release of calcium into and from the sarcoplasmic reticulum. *A*, Before the addition of dantrolene. *B*, Effect of dantrolene inhibits calcium release from the sarcoplasmic reticulum. (*From* Van Winkle WB: Calcium release from skeletal muscle sarcoplasmic reticulum: Site of action of dantrolene sodium. Science 193:1130–1131, 1976; with permission.)

reported as "triggering" despite oral[29] or IV[105] administration of dantrolene preoperatively. There remains no evidence that prophylactic dantrolene effectively prevents MH reactions.

The IV pretreatment dose of dantrolene does not produce any adverse cardiovascular effects and does not affect respiratory variables such as peak expiratory flow rate, vital capacity, end-tidal CO_2 and respiratory rate.[89] It is interesting that dantrolene at such doses causes peripheral muscle weakness as evidenced by marked diminution of both twitch response and grip strength.[40] Fatigue is also a common problem for 24 to 48 hours. Consequently, common sense dictates that patients receiving dantrolene preoperatively or intraoperatively will require a smaller dose of muscle relaxant, and ambulation is preferably avoided in the first 24 hours, and then performed cautiously for at least 48 hours. Also, such doses of dantrolene in awake patients cause dizziness, lightheadedness, and occasionally nausea. Difficulty in swallowing may also occur in the first 24 hours of its administration.

Other measures useful in avoiding triggering MH are (1) moderate to heavy premedication with tranquilizers (no phenothiazines,[45] but barbiturates and opiates may be used, and in children rectal methohexital is a good choice); (2) a balanced anesthetic technique (nitrous oxide–oxygen, barbiturate, opioid tranquilizer, and a nondepolarizing muscle relaxant) using an anesthetic machine flushed free of inhalational anesthetics[84] (ketamine[26] and propofol[43, 100] have not been reported as "trigger" drugs, but desflurane[121] and sevoflurane[112] have been associated with the development of MH, as have all potent inhalation anesthetic drugs); (3) careful monitoring (the most important aspect of management; all changes in heart rate should be carefully followed, and end-expired CO_2 analyzers and a temperature monitor should be used); (4) use of all local anesthetic drugs whether amides or esters (Dershwitz et al[25] have reviewed the literature and have not found a report of MH caused by any local anesthetic drug); and (5) availability of dantrolene.

Although caffeine induces contracture responses in vitro, it seems that these effects do not apply to related compounds, such as theophylline or aminophylline.[39]

MASSETER SPASM

In the 1970s, masseter spasm after IV succinylcholine was recognized as a possible marker for MH.[27] If this tetany of the jaw muscles was appreciated by the anesthesiologist, the procedure, if elective, was to be immediately terminated. A strong correlation between succinylcholine-induced masseter spasm and malignant hyperthermia was described.[33, 103, 110] In some patients, no cause was identified,[33] although a complete differential diagnosis must be considered.[69]

The inability to open the heavily sedated patient's mouth after the administration of succinylcholine is a subjective judgment. The patient can be slightly resistant or there can be active tetany. Further succinylcholine administration does not result in paralysis of these muscles. The other skeletal muscles of the body can be tetanic but more commonly are paralyzed. The increased masseter muscle tension may last from a few minutes to half an hour. All patients can be ventilated with a face mask despite the rigidity and the inability to open the mouth because the chest wall is relaxed. Simple bag and mask ventilation will therefore sustain oxygenation until the masseter muscles relax. Interestingly, most episodes do not progress to MH reactions, and no patients have died following isolated masseter spasm.

The report that has upset this neat scenario was presented by Van Der Spek et al.[117] These authors found *routinely* increased tension in the muscles of mastication following IV administration of succinylcholine. Similar results were observed in adults.[67] Currently, there is no physiologic explanation for this phenomenon. How can a depolarizing muscle relaxant that induces paralysis in all skeletal muscles by a well-determined mechanism produce increased tension in all subsets of skeletal muscles at the same time? Is there an intracellular action of succinylcholine in the muscles of mastication and, possibly, the eye muscles that override the neuromuscular junctional effect of the drug? How should we now interpret masseter spasm or tetany? Is it a normal phenomenon, a normal or abnormal variant, a developmental occurrence—or should we still consider increased tension as pathologic? Currently, there are no definitive answers to these questions.[19, 113, 118] It may be that developmental and hormonal factors influence the occurrence of masseter spasm.

However, the previous relationship of succinylcholine-induced masseter spasm and a positive muscle biopsy (more than half the patients studied have tested positive) needs to be carefully re-examined. The masseter muscles examined in one study[16] have a predominant type I content. Myoglobinemia after succinylcholine has been noted to be more frequent in childhood after halothane (40% incidence) than after pentothal (20% incidence).[107] Puberty lowers the frequency after both drugs to 3%. Also, two retrospective analysis of rigidity after succinylcholine (as determined subjectively) was 1% in patients induced with halothane.[19, 110] This incidence in one of the reports was 3% if strabismus was present.

How should we proceed when masseter spasm occurs after succinylcholine administration? Previous studies recommended aborting the anesthetic and proceeding at a later date.[103, 110] More recently, a retrospective analysis of 68 patients recommended proceeding with the anesthetic as though the event had not occurred.[73] Because there is little information now available to make a sound judgment, caution is a sensible refuge. After observing the patients for 15 to 20 minutes to be certain the symptoms and signs of an MH episode do not occur, the anesthetic may be continued, using a nontriggering technique, or halted and the surgery postponed. This decision should be made concurrently by the anesthesiologist, the surgeon, and the family. If any of the three is hesitant to proceed, then the conservative approach seems appropriate. With any decision, the patient should be carefully monitored, remain in-house overnight, have serum CPK levels measured at the time of the episode and again at 8, 12, and 24 hours postoperatively, have all urine samples tested for myoglobin in the first day, and have a thorough, formal neurologic examination with electromyography to establish a baseline. Every effort should be made to establish a diagnosis.[69] As our knowledge of masseter spasm increases, our management of this disorder will similarly improve. It behooves us to keep an open mind until this puzzling phenomenon is explained.

GENETICS

MH is an inherited metabolic defect best described as autosomal dominant, with reduced penetrance and variable expressivity.[31, 44, 59, 60] Reduced penetrance implies that fewer offspring are affected than would be predicted by a totally dominant pattern. Variable expressivity implies differing susceptibility between families, with little variation within the same family. However, not all patterns of inheritance fit this description, and consequently it is proposed that malignant hyperthermia is transmitted by more than one gene and more than one allele.[31, 59, 60] Recent familial studies have linked the MH defect to chromosome 19[80, 81, 83] (Fig. 2).

ETIOLOGY AND MECHANISM OF OCCURRENCE

Most of the investigative work on the pathophysiology of MH has been performed on the pig. Swine breeders and veterinarians have long known that

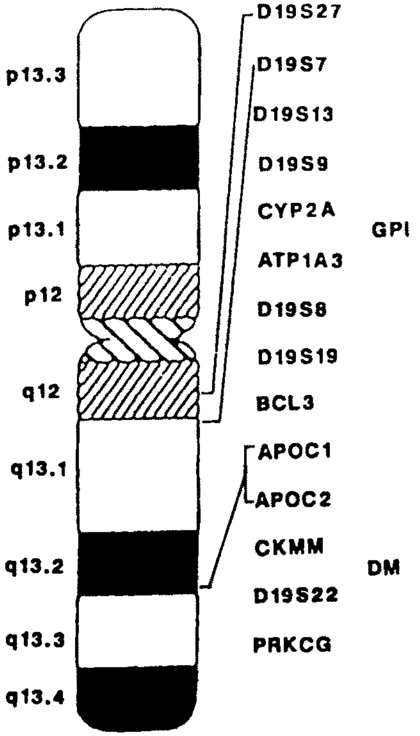

Figure 2. The location of MH susceptibility to DNA markers from 19q12-13.2 region of human chromosome 19 as reported by McCarthy et al[83] has a maximum likelihood of 450,000:1 favoring linkage of susceptibility to the cytochrome p450 (CYPZA) locus. The location of a DNA marker for Duchenne's muscular dystrophy is shown by DMD.

certain strains of pig, when exposed to stresses related to slaughter, accelerated their metabolism; it was also found that the muscle in these pigs deteriorated into pale, soft, exudative pork.[30] Further observations led to the conclusion that porcine stress syndrome and MH are practically the same genetic disease.[106] Episodes of both syndromes demonstrate the same biochemical changes: fever, acidosis, cyanosis, mottling, rigidity of muscles and rhabdomyolysis, cardiac arrhythmias, and eventually shock. Consequently, some porcine pedigrees particularly susceptible to MH have been identified (e.g., Landrace, Pietrain, Poland, and China); these strains provide a model for the study of the human syndrome.[5] Much of our knowledge of the pathophysiology of this disease and the eventual identification of the specific treatment of MH has been based on studies of this animal model.[38, 49, 50]

The etiologic defect responsible for MH has not yet been identified. Several hypotheses have been proposed. One relates to the calcium release channel of the terminal cisternae of the sarcoplasmic reticulum.[83] This channel is also termed the *ryanodine receptor* (named for the discovery of a potent muscle toxin in the nineteenth century). Louis and Mickelson[77] have found a greater affinity in vitro for ryanodine by human MH-susceptible sarcoplasmic reticulum than by normal human sarcoplasmic reticulum. This was attributed to a gene coding mutation for this channel.[81] Purification of the receptor demonstrated a similar increased affinity to ryanodine by the MH receptor in pigs.[87] Hogan et al[55] found human and pig receptor function similar. This seemingly strengthens the argument for a common etiology. Proteolytic digestion revealed a distinct difference in immunostaining of the peptides derived from the calcium release channel between MH and normal pigs. Other work has shown a greater sensitivity to caffeine of single calcium release channels of human MH patients when compared with normals.[93] This mirrors the effect at the whole cell level, because caffeine sensitivity has been a hallmark of MH susceptibility. Recent evidence suggested that, at least in one biopsy-positive family, genetic linkage between the ryanodine receptor and MH genes was demonstrable, albeit in the presence of more stringent muscle biopsy cisterna than is currently used.[71, 80] Human molecular genetic linkage studies have shown linkage between MH susceptibility and DNA markers on chromosome 19[83] in an area that is responsible for the activity of a hormone sensitive lipase and has led to another etiologic hypothesis.[37] Skeletal muscle free fatty acid metabolism is reported as abnormal in MH. The source of the elevated free fatty acids (FFA) appears to be triglycerides. The hormone-sensitive lipase is an enzyme system that mobilizes FFA from triglycerides. The elevated FFA are suggested as responsible for the increased calcium release and decreased sarcoplasmic reticulum calcium uptake.

The target organ in MH is skeletal muscle.[30, 31, 59] The disturbance of calcium flux from the sarcoplasmic reticulum is membrane.[8, 13, 47, 58, 61, 62, 74, 97, 115] To understand the pathophysiologic changes that occur in skeletal muscles during an episode of MH, it is important to understand the basic physiologic changes that occur during normal contraction of skeletal muscle.[90]

The nerve impulse, through its action on the neuromuscular junction, creates a chain of events that leads to depolarization of the muscle. The muscle action potential spreads on the surface of the muscle membrane from its center to its periphery. The action potential is transmitted to the interior of the muscle fiber by way of the T tubule system (Fig. 3). When it reaches the terminal sac of the sarcoplasmic reticulum, it causes a release of the calcium ion in the cytoplasm. Ionized calcium can also be released from the sarcolemma and mitochondria. Ionized calcium bound to calmodulin initiates contraction by removing tropomyosin-

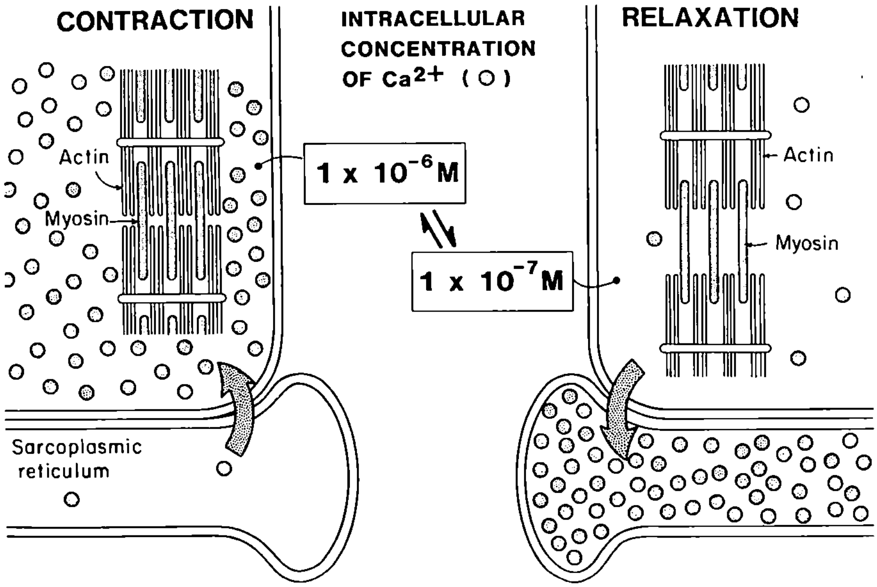

Figure 3. Acting myosin movement during calcium-stimulated muscle contraction. Biochemically, the relaxation phase is the energy-using process, and contraction is a more passive event. It is the failure of lowering myoplasmic calcium, which occurs normally during the relaxation phase, that leads to the development of MH in a patient.

troponin inhibition, which allows the actin filaments to slide across the myosin filaments, contracting the muscle fiber.[115]

During relaxation the calcium that was released during contraction is pumped back into the sarcoplasmic reticulum, the sarcolemma, and the mitochondria. This restores the tropomyosin-troponin inhibition, allowing the actin and myosin filaments to separate, lengthening the muscle fiber. This is an energy-requiring process provided through the generation of adenosine triphosphate (ATP) in the mitochondria.

The pathogenesis of malignant hyperthermia involves a defect in the uptake and/or storage of intracellular calcium. The main defect lies in the inability of the sarcoplasmic reticulum to store calcium. This is evidenced by an increase in myoplasmic free calcium.[20] At resting levels the ionized calcium (Ca | m+ | m+) levels are three or four times normal.[74] Upon triggering of MH, the intracellular Ca | m+ | m+ increases up to 17 times.[62]

The elevated myoplasmic calcium level (1) activates ATPase, thus accelerating the hydrolysis of ATP or ADP, (2) inhibits troponin, thus permitting a biochemical contraction to occur, and (3) activates phosphorylase kinase and glycogenolysis, with resulting production of ATP and heat. As the calcium levels further increase, calcium diffuses into a secondary storage site, the mitochondria. This Ca | m+ | m + infusion stimulates aerobic activity within this organelle, as well as the sarcolemma. The ATP will be diminished by this furious enzymatic activity; therefore, the supply of high energy bonds will diminish and the hypermetabolic muscles will be unable to cope completely with the energy demands by means of aerobic metabolism. Consequently, the muscle will resort to anaerobic metabolism, and lactic acid will start to accumulate.

As a consequence of this, the metabolic rate is accelerated, causing a high rate of oxygen consumption, as well as heat and carbon dioxide production. The circulation may allow heat dissipation early in this sequence, but soon, in an effort to supply the increased demands for oxygen to the muscles, peripheral vasoconstriction can occur, blood is shunted away from the skin, and body temperature may rise dramatically.[99]

Because of the marked increase in the oxygen uptake of muscle cells, the venous blood will therefore be markedly desaturated of oxygen, and will have a high CO_2 concentration (respiratory acidosis) owing to the enhanced intracellular processes; lactic acidosis (metabolic acidosis) results when oxygen demands outstrip oxygen delivery. These factors have clinical importance because the earliest change in the fulminant hypermetabolic state will be mirrored on the venous side of the circulation as a respiratory acidosis. It is therefore very helpful to obtain a venous blood sample when seeking a diagnosis of malignant hyperthermia. End-tidal CO_2 monitoring will serve a similar purpose. Continuous measurement has enabled our pediatric anesthesia group to diagnose MH in two children.[3]

The continued uncontrolled contraction of a large group of muscles can lead to the clinically observed rigidity.[20, 56, 99] This most often occurs early after administration of succinylcholine, but it may also be seen later. In the late stages of a full-blown MH episode, development of rigidity is attributable to the temperature rise within the muscle cell.[42]

The actomyosin ATPase enzyme system ends muscle contraction. If there is an enzyme malfunction, then continued contraction leads to rigidity. Our laboratory has noted a relationship between the clinical rigid form and markedly lowered function of actomyosin ATPase. The presence or absence of rigidity may well be related to the level of free intracellular calcium. In animal studies, calcium concentration that did not quite reach the threshold for contraction, i.e., 1×10^{-7} M, did not result in rigidity, although the hypermetabolic aspects of the syndrome were present.[76] From other reports and our own data in pigs, the end-tidal CO_2

monitor is the most sensitive and useful monitor for the diagnosis of a hypermetabolic event, and in MH it is elevated before any clinical change in pulse or respiration.[3, 28, 72, 78, 106, 116]

The pulse oximeter can also be of value as a monitor for an MH reaction, because desaturation will occur at intermediate and lower inspired oxygen concentrations during anesthesia owing to an increase in the venous extraction of oxygen. Both of these monitors are useful in the post-treatment monitoring of an MH episode.

Muscles are the main tissues involved in this syndrome; with a full-blown episode there may be massive swelling of the muscles, rhabdomyolysis, and a massive leak of potassium and calcium outside the cells. Early on, the hyperkalemia can be massive, and arrhythmias can quickly progress to cardiac arrest. Hyperkalemia is the major cause of mortality early in the syndrome. Calcium channel blockers have produced fatal, evanescent increases in serum potassium in swine and thus are contraindicated in the therapy of MH.[54, 104, 109] With adequate treatment, these electrolyte abnormalities reverse spontaneously.

The cardiac arrhythmias observed in this syndrome are nonspecific. Several factors contribute to their occurrence: hyperkalemia, fever, acidosis, hypoxia, and autonomic hyperactivity. There is also the possibility that the syndrome directly affects cardiac muscle.

If the patient survives, other complications may occur, including consumption coagulopathy, hemolysis, myoglobinemia, and myoglobinuria; the latter may lead to renal failure.

The cause of death in this syndrome is variable and related somewhat to the particular time that death occurs. In the initial few hours, it is most probably from ventricular fibrillation. If death occurs several hours later, after a prolonged attempt at resuscitation, it may be due to pulmonary edema, coagulopathy, acid-base imbalance, or electrolyte imbalance. In the predantrolene days, recovery with supportive therapy was accompanied by a transient sharp decrease in plasma potassium concentrations. This intracellular redistribution was attributed to a return toward normal of plasma pH. In the next 6 to 8 hours, a slow increase in plasma potassium occurred that was extremely sensitive to any IV potassium supplementation. If death occurred days after the episode, it was more likely to result from multiple organ failure, brain damage, or renal decompensation.[8]

A coagulopathy, usually disseminated intraocular clotting, can occur. Early dantrolene therapy will avoid this complication.

It is interesting that the height of the fever has no specific predictive effect on the outcome.[17] The author's first patient had a temperature elevation of greater than 43.8°C (110.8°F), with cardiac arrest and a plasma potassium level of 14.9 mmol/L, all occurring within an 18-minute period.[108] Approximately 2 hours later, this patient was trying to vocalize her desire to be extubated. She eventually made a complete recovery. In spite of this markedly elevated temperature, no brain damage ensued. This contrasts with the widely held view that brain damage inevitably occurs at these temperatures.

THE FAMILY

After an episode of MH, dealing with the family of the patient becomes a major challenge for the anesthesiologist. Most importantly, the family needs information and support. Frequently, the stunning effect of this complication will deter the anesthesiologist from close contact with the family; yet, the psychologic and legal consequences for both the family and physician of such inaction, even with a good outcome of the MH episode, can be catastrophic.[48]

Genetic testing may replace muscle testing as the laboratory determinant of MH susceptibility. Until a uniform genetic test is available, it seems reasonable to document MH susceptibility by a muscle biopsy at an appropriate interval after the reaction. It will then be necessary to determine which branch of the family is susceptible. Once these two goals have been accomplished, further testing within the family can be performed. Biopsies of these other family members should be attempted only after informing them that the test is not a medical necessity; anesthesiologists will treat the entire family as positive in the absence of muscle biopsies, and in some instances, regardless of biopsy results.[2] Muscle biopsy during incidental surgery in family members makes eminent sense. The only restriction is the withholding of dantrolene sodium and droperidol before excision of the muscle specimen. These two drugs have been shown to "normalize" abnormal responses of the muscle specimens in MH-susceptible individuals.[45, 46]

A common practice in planning anesthesia for family members of a known MH family is to request muscle testing separately before the procedure. In most instances, because a balanced technique will be used whether the results are normal or positive, it seems easier, and less expensive, for the patient to have a muscle biopsy taken at the time of the planned elective operation.

The long-term relationship between the anesthesiologist and the family of an MH survivor, continued education, and availability of the anesthesiologist are important factors. The family needs literature; they need their questions answered. They need to know of the support group, the Malignant Hyperthermia Association of the United States. This organization maintains a hotline number (209-634-4917, ask for Index Zero) that is available 24 hours a day to physicians, for information during emergency situations, for follow-up advice, and to MH families.

Most of the time, MH occurs in situations where it is least suspected. With a careful history, however, information can be obtained indicating that one of the patient's relatives has had a complicated anesthetic history. There are also some disorders that have an inconstant association with MH.[46] These diseases include muscular dystrophies; of these, the Duchenne type is the most severe and rapidly progressive and seems to be the one most commonly associated with MH.[15, 47, 88] Other associated diseases may include central core disease and neuroleptic malignant syndrome.[22, 23, 41] Neuroleptic malignant syndrome has not been described clinically in a patient who has experienced an episode of MH. Also, biopsy studies have presented varying results in relating these two syndromes.[18, 68, 75, 102] Although symptoms such as ptosis or squint have been suggested as associated with MH, or such skeletal deformities as scoliosis or kyphosis, historical associations have not been successful. The reported literature[34, 51] and our own history taking demonstrate the only helpful question in a medical history relates to previous difficulty or death in the family during anesthesia. A history of symptoms such as muscle cramps were similar for control and MH (Hill and Ryan, unpublished data). In adults, intolerance to caffeine is one of the distinctive symptoms. Using norepinephrine turnover as an index of peripheral sympathetic nerve function, no difference was noted between age-matched controls and MH-susceptible patients.[91]

Several other tests can be performed to evaluate susceptibility, but none of them are conclusive. The most common is serum CPK. It is elevated in many conditions[10, 32] and even at rest in 60% to 70% of susceptible patients.[57] The usefulness of CPK in MH diagnosis is predicated on lack of other muscle disease that would explain the elevation, as well as the peak of the elevated enzyme. Levels above 20,000 in suspected patients who have had biopsies have been associated uniformly with a positive diagnosis.[66] We have set an arbitrary level of a tenfold increase in CPK as being diagnostic of MH in otherwise unexplainable situations. Although CPK is a useful measure if markedly elevated, a lack of CPK elevation does not exclude the diagnosis of MH.

Another blood test that has been advocated for the detection of MH is the halothane-induced platelet ATP depletion test.[114] It seems to be satisfactory in the hands of the original authors but does not seem to be reproducible by other researchers.[44] In pigs, a single study of calcium permeability in platelets and the effect of halothane distinguished MH pigs from normals when utilizing a fluorescent calcium indicator dye.[79] Abnormalities in similar dye studies in pig lymphocytes and monocytes have been reported.[63, 95] Conflicting data regarding the differing responses of MH porcine red blood cells and normals have also been published. Ohnishi and Sadanaga[96] found a distinct separation in the two categories, whereas Halsall[52] was unable to repeat the results. Currently, there remains no blood test to confirm the diagnosis of MH.

DIAGNOSTIC TESTING

The diagnosis of MH is primarily determined by the clinical responses. Once even a weak set of symptoms have been diagnosed as MH, the patient and his or her family usually are considered positive by all physicians ever after. This may seem unjustified in some circumstances, and perhaps not medically or ethnically correct, but it is the reality of present day medicine. It is interesting to note that in a population referred to us, 50% of family members of known MH-susceptible patients may themselves be susceptible to MH, which is consistent with the autosomal mode of inheritance. This supports the need for caution in administering anesthesia to members of a family in which one person is susceptible.

Muscle biopsy specimens have been used to determine the presence or absence of a consistent marker in muscle function associated with MH. One test that has gained acceptance by several laboratories is quantitation of the forces of muscle contracture following exposure of the biopsy sample to halothane, caffeine, or both. If masseter spasm presents a physiologic conundrum, the present interpretation of diagnostic muscle testing is a maelstrom of confusion. In Europe, all testing follows a similar protocol.[35] Testing defined patients as positive (two tests positive), equivocal (one test positive), or negative. Approximately 15% of patients studied are equivocal. This category has been recently questioned.[7] In North America, each laboratory and its own experience serves as interpretive criteria.

In an attempt to unify current methods of testing, Larach and Landis[65] reported on 176 "normal" specimens studied on the 11 North American laboratories. Using a "common" definition of *normal*, the incidence of false-positive diagnosis in these 176 patients ranged from 10% to 70%, with a mean of 38%.[65] This result does not examine the present unilateral criteria for diagnosis, but shows that standardization of the criteria used to establish a positive muscle biopsy for MH in North America is long overdue.

The basis for halothane, caffeine contracture testing (HCCT) is an "abnormal" response by freshly excised skeletal muscle to halothane, caffeine, or both. This excised muscle is placed on stretch in a bath at 37°C. After optimal length tension has been determined, halothane, caffeine, or both are added, the muscle is stimulated supramaximally, and the contracture amplitude is measured.[2, 33] Resting membrane potential is critical in the response to caffeine.[1]

A vigorous in vitro contracture of a skeletal muscle specimen to halothane, and a reduced contracture threshold to caffeine, can identify the donor as susceptible to MH (Fig. 4). The responses to 2 mM caffeine and to less than 2% halothane were the only test results that unequivocally discriminated between susceptible and normal control subjects.[112] However, simultaneous exposure to both halothane and caffeine produces considerable overlap between normal and known MH-susceptible patients, indicating that the combined test is too sensitive (Fig. 5).

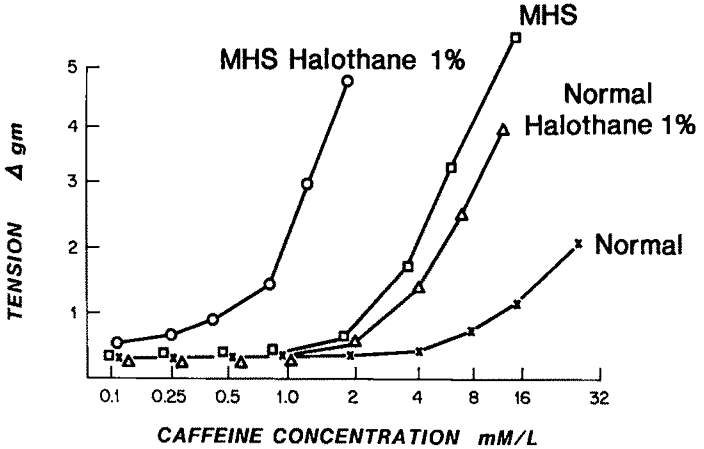

Figure 4. This idealized graph demonstrates the response of various classifications of patients to muscle testing by caffeine contracture. Clinically, there may be an overlap, which clouds the diagnosis in an individual case.

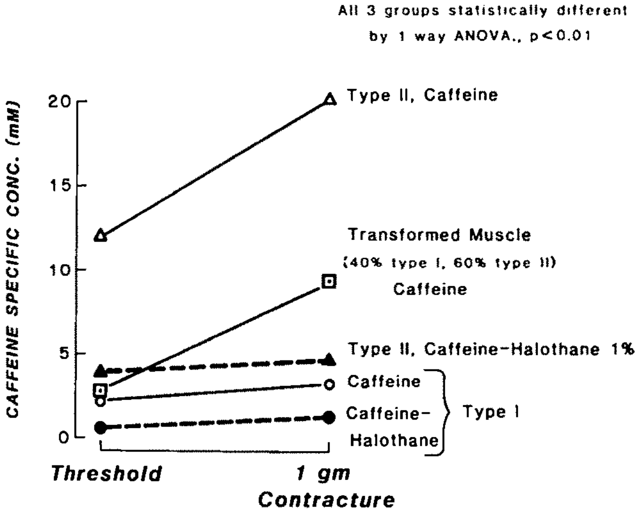

Figure 5. This figure presents the effect of fiber type on caffeine contracture studies. Pure type I and II fiber samples differ in their contracture response to caffeine and halothane-caffeine. Prolonged electrical stimulation causes type II fibers to become type I. After 3 months of low-grade stimulation, the transformed fiber content is 60/40\6, as shown above. The quantification of the muscle fiber type of each individual biopsy specimen is an important determinant in evaluating susceptibility to MH. (*From* Britt BA, Kalow W, Gordon A, et al: Malignant hyperthermia: An investigation of five patients. Can Anesth Soc J 20:431–67, 1973; with permission.)

This conclusion is controversial depending upon the laboratory involved. Any widely sensitive test to confirm an unequivocal diagnosis either positive or negative will have a gray zone. In MH, the problem is the patient with clinical evidence of MH who tests unequivocally negative with a muscle biopsy. As a result, many clinicians disregard the results of the negative biopsy.[2] This wide spectrum of MH susceptibility has been observed in both humans and pigs.[92] Therefore, most laboratories tend to take the conservative approach, favoring a false-positive diagnosis because the consequences of a false-negative result are much more serious than for the former. It is better to treat the patient as if he or she has MH and avoid all triggering agents than to assume the patient is negative and end with catastrophic complications.[2] This approach, however, has led to a reluctance by some clinicians to send patients for muscle biopsies and to assume the patient has MH. Genotyping for MH may provide the definitive diagnosis.

SUMMARY

Malignant hypertension is a hypermetabolic event that can be triggered in genetically susceptible individuals by anesthesia. It has occurred in newborns and in the elderly.[86, 111] With constant vigilance, it can be treated adequately with a successful outcome. However, if neglected, undiagnosed, or mistreated, it can lead to disastrous consequences. Recent advances in understanding the genetic defect may provide the much needed insight into this most puzzling, and potentially fatal, clinical syndrome.

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Editor *(Name and Complete Mailing Address)*

June Eberharter, W.B. Saunders Company,
Curtis Center, Independence Square West, Phila., Pa 19106-3399

Managing Editor *(Name and Complete Mailing Address)*

Barbara Cohen-Kligerman, W.B. Saunders Company,
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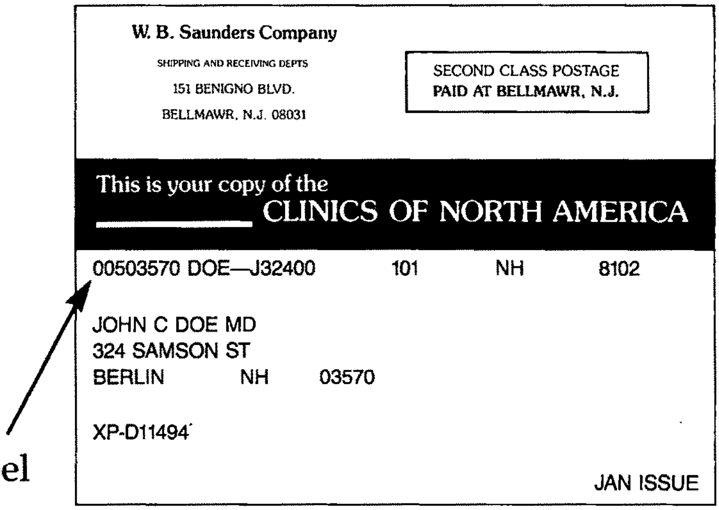

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